

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021825Orig1s000**

**MEDICAL REVIEW(S)**

MEMORANDUM      DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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Date:            September 20, 2011

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                  Division of Hematology Products  
                  Office of Hematology and Oncology Products

Subject:        Medical Team Leader Secondary Clinical Review  
                  Ferriprox (deferiprone), resubmission received 4/14/2011; amended study  
                  report received 7/25/2011

To:              NDA 21-825

Ferriprox (deferiprone) is an orally active iron chelator developed for use in treating iron overload. This is the second review cycle for this product. The NDA was initially submitted 1/29/2009 for the indication, “treatment of iron overload in patients with transfusion-dependent thalassemia and for treatment in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate”. A complete response (CR) letter was issued on 11/30/2009. The current resubmission (received 4/14/2011) seeks approval of deferiprone for the indication: “for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate.” The proposed dose is Ferriprox is 25 to 33 mg/kg body weight, orally, three times a day for a total daily dose of 75 to (b)(4) mg/kg body weight.

**Background**

Patients with certain inherited anemias (importantly  $\beta$ -thalassemia and increasingly sickle cell disease in the U.S.) require frequent transfusion of red blood cells beginning at a young age to offset anemia that occurs because of inability to manufacture normal hemoglobin. Normal dietary absorption is about 1 mg daily which maintains a total body iron of approximately 3 to 5 grams in adults. One unit of packed red blood cells contains about 200 mg of iron. Because the body has no physiologic mechanism to excrete excess iron, repeated red blood cell transfusions over time result in massive iron overload. The excess iron becomes deposited in tissues and causes tissue damage due to iron-catalyzed peroxidation of membrane lipids and leads to morbidity and often eventually mortality, mainly due to cardiac damage. The liver and endocrine organs also are notably affected. Assessment of liver iron content (LIC) has been the generally accepted standard for

assessment of body iron burden; however, serum ferritin, a nonspecific parameter, is commonly followed clinically.

Currently available treatment options for management of iron overload due to transfusions include Desferal (deferoxamine mesylate), an injectable iron chelator approved in 1968 and Exjade (deferasirox), an orally active iron chelator approved in 2005.

Deferiprone binds iron in a 3:1 complex which is then excreted in the urine. The drug was first administered to humans in 1987, was approved in the European Union in 1999 and currently is approved in 61 countries, mostly for the indication of the treatment of iron overload in patients with thalassemia major when deferoxamine therapy is contraindicated or inadequate. The U.S. IND for deferiprone (IND 45724) was opened 7/15/1994. Orphan Drug designation was granted on 12/12/2001 and Fast track designation was granted 1/26/2004. The fact that the drug was granted Fast Track designation reflects the serious nature of the condition for which the drug is intended to be used and the fact that at the time the designation was granted the only therapeutic option for these patients was deferoxamine which must be administered via continuous subcutaneous infusion over many hours each day and which, therefore, is difficult for many patients to comply with and/or tolerate.

For detailed background please refer to Dr. George Shashaty's Clinical Review (10/19/2009) and my Cross-Disciplinary Team Leader (CDTL) review (11/25/2009; addendum 12/31/2009) of the first cycle NDA submission.

### **Complete Response (CR) Letter**

For the initial NDA submission the sponsor provided a single randomized controlled trial (Study LA16-0102) comparing the use of deferiprone versus the use of deferoxamine in removing excess cardiac iron in subjects with thalassemia major. The study used a primary efficacy endpoint that employed magnetic resonance imaging of the heart (cardiac MRI) with measurement of a parameter termed T2\* (T2 star) to evaluate extent of iron overload and effectiveness of chelation therapy. The primary efficacy analysis of change in cardiac MRI T2\* from baseline to 12 months showed a 3.9 msec increase in cardiac MRI T2\* in the deferiprone treatment group (N=29) and 2.3 msec increase in the deferoxamine treatment group (N=32). The study did not find a significant correlation between change in cardiac MRI T2\* and measures of cardiac function and there were no differences between treatments in change in liver iron concentration (LIC). A retrospective supportive study, LA 12-9907, evaluating occurrence of cardiac disease also was submitted. Consultations were obtained from the Center for Devices and Radiological Health (CDRH) (S.S. Rajan, Ph.D., dated 7/26/2009 [signed hard copy 11/4/2009]) and the Division of Medical Imaging and Hematology (Dr. M. Fedowitz, 4/15/2009 [signed 4/28/2009]) regarding the use of MRI for imaging cardiac iron and from the Division of Cardiovascular and Renal Products (DCRP) (Dr. S. Targum, 4/20/2009) regarding significance of measured changes in cardiac function parameters in

the LA16-0102 study and these consultative reviews were considered in the clinical review of the application. Safety concerns for the drug were agranulocytosis (which occurred in 1.7% of patients in the deferiprone clinical studies), hepatic toxicity, gastrointestinal adverse reactions, arthropathy, cardiac (a case of torsades de pointes), neurological, and miscellaneous reactions. Also, (based on non-clinical studies) deferiprone is genotoxic and teratogenic.

Clinical deficiencies listed in the 11/30/2009 CR letter and information needed to address the concerns were as follows:

1. The application contains insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling and lacks substantial evidence of efficacy from adequate and well-controlled investigations. Listed below are our requests for additional data, followed by a summary of the basis for these requests.
2. A decrease in the cardiac content of iron, as measured by magnetic resonance imaging (MRI) T2\* alterations, was the proposed treatment effect in the single confirmatory study intended to verify deferiprone safety and efficacy. Listed below are requests for additional information if you use this endpoint in any future regulatory submissions:
  - a. Supply data from at least one additional prospective, randomized, controlled clinical study that verifies the proposed deferiprone treatment effect.
  - b. Supply data that verify the clinical meaningfulness (e.g., improved survival, symptoms, functional status or other clinical benefits) of incremental changes in cardiac MRI T2\* values. These data should establish the minimum millisecond increase in T2\* that is indicative of a clinical benefit.
  - c. In developing subsequent clinical studies, we encourage you to enroll pediatric patients with transfusional hemosiderosis. Data within the submitted confirmatory study were obtained entirely from adult patients.
3. Submit data that verify the absence of a mortality disadvantage when deferiprone is administered over a prolonged time period. These data could be obtained from follow-up survival information for all patients enrolled in Study LA-01 ("Randomized Trial of Deferiprone and Deferoxamine in Thalassemia Major") and Study LA-16-0102 ("Randomized Trial Comparing the Relative Efficacy of Deferiprone to that of Deferoxamine in Removing Excess Cardiac Iron in Thalassemia Major Patients"). Alternatively, supply data from other randomized, controlled studies that allow an assessment of survival in comparison to a clinically appropriate control therapy. The need for survival data cannot be addressed by the submission of uncontrolled study data or data from historically controlled/observational-type studies.
4. Submit data that more thoroughly assess the arrhythmogenic potential of deferiprone. In addition to any other information, supply data from an assessment of the effect of deferiprone and its primary 3-O-glucuronide metabolite on the electrocardiographic QT interval in patients and/or healthy volunteers.

5. FDA inspectional findings could not fully verify the accuracy of data submitted by you for Study LA-01, with respect to the Toronto, Canada clinical site. The principal investigator at that site was Dr. Nancy Olivieri. We understand that you terminated that study site in May 1996, prior to study completion. Our comments below pertain solely to data that was generated at that study site prior to the termination of the site. Supply information that addresses the items listed below:

- a. A Good Clinical Practice (GCP) inspection of Dr. Olivieri's data revealed discrepancies between superconducting quantum interference device (SQUID) values verified by source documents at the site in comparison to the data submitted to the NDA.

Address these discrepancies.

- b. The GCP Inspection of Dr. Olivieri's data also revealed that the liver biopsy iron concentration values reported in the NDA listings as provided by you in 2.2.1 could not be verified by source documents, because the source documents were not available.

Provide all source documents to support the iron content as measured by liver biopsy.

6. With regard to Study LA-01, there appear to be inconsistencies in your analyses of the data and the exclusion of certain subjects and data points from the analysis. Specifically:
  - a. Per Data Listing 2.2.2 in the NDA, several iron concentration data points were excluded from analysis and the rationale for each exclusion was provided in this data listing. However, the rationale for exclusion was inconsistently applied in your analyses. For example, Subjects 42, 43, 51, and 55, had all of their iron concentration data excluded from analyses because "patient[s] did not complete 24 months of chelator therapy." However, Subjects 25, 34, 37, and 59, were included in your analyses (as provided in Data Listing 2.2.1) even though these subjects apparently did not receive 24 months of chelator therapy.

Address this inconsistency.

- b. We also note that Table 12.2, Patient Listing of Discontinued Patients, includes information for subjects from Dr. Olivieri's site from 1997, which was after the study site was terminated. Therefore, you appear to have access to at least some data collected after termination of the site.

Confirm that all relevant data in your possession at the time of NDA submission, regardless of whether those data were generated after termination of the study site, were included in the application.

We cite the following information as the basis for the clinical requests listed above:

7. You provided data from a single, controlled trial as confirmatory evidence of deferiprone efficacy and safety (Study LA-16-0102). In this study, 61 adult patients were randomized to therapy with either deferiprone or deferoxamine.

- a. Regarding efficacy, you claimed that greater increases in cardiac magnetic resonance measures of T2\* were observed in the deferiprone group than in the control group, a primary endpoint outcome which you proposed as indicative of a decrease in cardiac iron and a clinical benefit. However, the supplied data did not establish the specific clinical benefit attributed to the increase in T2\* measurements. Additionally, we do not regard the primary endpoint result as a robust observation due to the study's relatively small sample size, which precluded subset and other exploratory analyses.

Secondary endpoints also were not consistently corroborative of the primary endpoint result. For example, changes in serum ferritin and liver iron concentration were not significantly different between the two study groups.

- b. Regarding safety, adverse events related to elevation of serum alanine aminotransferase levels were reported in 38% of the deferiprone group but in only

13% of the deferoxamine group. In the context of additional concerns (below), this observation signals the potential for deferiprone-induced liver toxicity.

8. The supplied supportive study (LA 12-9907) used an uncontrolled design and statistical features consistent with an exploratory study. Hence, this study was incapable of verifying deferiprone efficacy and safety.
9. The other supplied clinical data are of very limited value to verification of deferiprone effects, particularly when the proposed confirmatory study failed to verify safety and efficacy. The supportive data included the occurrence of an important cardiac arrhythmia (torsade de pointes) that was assessed by a cardiologist as possibly related to deferiprone therapy. Overall, the supportive studies contained numerous deficiencies, such as the use of retrospective designs, relatively small sample sizes, the lack of control groups, missing data and inconsistency in results. Post-marketing reports indicated the occurrence of agranulocytosis followed by death in 13 patients.
10. In consideration of the submitted data, complete and accurate submission of clinical data from Study LA-01 is relevant to the evaluation of deferiprone safety and efficacy because the sample size exceeded that of all other controlled studies. Study LA-01 is also of interest because it used a primary endpoint that has previously been accepted by FDA.

11. Published literature does not consistently support the efficacy or safety of deferiprone. Some studies have suggested loss of effectiveness over expanded time periods and others have suggested increased liver toxicity among patients who remain on prolonged deferiprone therapy (Blood 1998;91:295-300 and the New England Journal of Medicine 1998;339:417-423). We note that other reports have not cited these problems. In the context of the safety and efficacy deficiencies cited above, the inconsistency within the published literature underscores the importance of complete data submission from adequate and well controlled clinical studies that rigorously assess clinically meaningful outcomes, including overall survival.

Importantly, an additional prospective, randomized, controlled clinical study was recommended. Following issuance of the CR letter, further discussions with the applicant were held. Those discussions concluded that there still was an unmet medical need for iron chelating agents. It was considered that possibly data for deferiprone could support an application for 2nd or 3rd line use of deferiprone for patients in whom the existing therapies are inadequate. To support use in this more restricted population the sponsor reanalyzed data from the completed studies examining change in serum ferritin levels in patients identified as being inadequately treated with other iron chelators. The results of this reanalysis of the data are presented in the current resubmission as Study LA36-0310. Additionally, updated safety information has been submitted. A revised study report for LA36-0310 was submitted 7/25/2011 to incorporate patients from Study LA11. These current submissions have been reviewed in detail by Dr. George Shashaty (see review dated 9/16/2011).

### **Study LA36-0310**

Study LA36-0310 was a retrospective selection of a subset of patients from pooled previously conducted studies. All studies except for a single arm study (LA30-0307) of a deferiprone solution in pediatric patients with thalassemia and iron overload had been submitted in the initial NDA. The LA36-0310 study population consisted of patients with transfusional iron overload who were inadequately responsive to previous iron chelation treatment defined as having one or more of the following: serum ferritin >2500 µg/L, cardiac MRI T2\* value <20 msec, and/or LIC >7 mg/g dry weight. Selected patients must have received chelation therapy prior to deferiprone. In addition, to be enrolled in the study for the primary efficacy analysis (change in serum ferritin), patients must have at least one serum ferritin value available for baseline prior to initiation of deferiprone therapy and at least one follow-up ferritin value within one year after starting deferiprone. (The 1 year value was the last available value up to 15 months after starting deferiprone). An Independent Committee was employed for selecting eligible patients. For data analysis the primary efficacy endpoint: was change in serum ferritin from baseline to end of study (up to 1 year of deferiprone therapy). Secondary efficacy endpoints included change in LIC and cardiac MRI T2\* from baseline to end of study (up to 1 year of deferiprone therapy). Treatment success for change in serum ferritin was defined by the sponsor as  $\geq 20\%$  decline in serum ferritin from baseline within 1 year of starting deferiprone therapy. For the secondary efficacy endpoints, the sponsor defined

treatment success similarly with cardiac MRI T2\* treatment success defined as  $\geq 20\%$  increase in cardiac MRI T2\* and in LIC treatment success defined as  $\geq 20\%$  decline in LIC.

**Results:** A total of 264 patients were eligible for the primary efficacy analysis. These patients were selected from 12 clinical studies, 11 of which had been included in the initial submission and 1 more recent study of deferiprone in pediatric patients with thalassemia. Four studies--LA-02/06, LA-04/06B, LA30-0307 and the Borgna-Pignatti study [Borgna-Pignatti C et al., Blood 2006; 107:3733-3737]-- accounted for 184 (70%) of the enrolled patients. LA-02/06 was a single arm safety study in patients with transfusion-dependent  $\beta$ -thalassemia and evaluated treatment with deferiprone for a planned total of 4 years (1 year in LA-02 and 3 years in LA-06) LA-04/06B was a compassionate use study in patients with thalassemia or other chronic iron overloaded conditions requiring iron chelation and for whom deferoxamine was inadequate or contraindicated. Treatment compliance was not assessed. LA30-0307 was a single arm study in pediatric patients with thalassemia and transfusional iron overload. It used a deferiprone solution administered orally for 24 weeks. Treatment compliance was said to "very high" based on drug exposure tables. Borgna-Pignatti et al was a published observational study that retrospectively evaluated cardiac morbidity and mortality with deferoxamine- or deferiprone-treatment in patients with thalassemia major. The paper states that no data were available regarding compliance. The mean age of the patients in the LA36-0310 study primary efficacy analysis was 20 years; 55% of these patients were females, 73% were Caucasian, 17% were Asian and 1% were Black. Among these patients 94.3% had  $\beta$ -thalassemia syndromes as the underlying disease; underlying disease was sickle cell disease in only 1.1% (2) of patients and was myelofibrosis in 1.9% (3) of patients. About 76.9% of patients received a deferiprone dose of 75 mg/kg/day, 17.8% received about 100 mg/kg/day and 5.3% received a dose of 50 mg/kg/day. Deferoxamine was the prior chelator in 250 (94.6%) of these patients. Eight (8) patients had received deferasirox (Exjade) only as prior chelator and 6 patients had received both deferoxamine and deferasirox prior to receiving deferiprone. Though the study was planned to assess deferiprone treatment for 1 year, only 27% of enrolled patients were treated for 1 year or longer. About 76% of enrolled patients had a treatment duration of at least 6 months.

The sponsor's primary efficacy analysis is shown below:

**Table 7.4.1-1 Overall success rate for serum ferritin – ITT population**

Study	Number of patients	Success rate (N, %)	95% C.I.
Overall	264	136 (52%)	(45%, 58%)

Source: [Appendix 12.1.9.2 Statistical Appendix 4.1](#)

A total of 136 (52%) of patients had a 20% or greater decrease in serum ferritin from baseline to end of study. Mean serum ferritin at study entry was 4416  $\mu\text{g/L}$ . The mean change in serum ferritin in the study was a decrease of 962  $\mu\text{g/L}$  and ranged from a

decrease of 10385 µg/L to an increase of 10002 µg/L. Success rates for patients from the various studies ranged from 26% in Study LA12-9907 (which contributed 19 patients) to 100% in Study LA15-0002 (which contributed 18 patients). Based on the sponsor's definition of treatment success as 20% of patients achieving a 20% or greater decrease in serum ferritin, treatment success for the study was declared for the primary efficacy endpoint.

Because some patients (about 11%) had received deferoxamine as well as deferiprone during the deferiprone treatment period of the study, an analysis was performed excluding these patients. The results of this analysis are shown below.

**Table 7.4.1-5 Subgroup analysis for success rate for serum ferritin: Ferriprox Monotherapy – ITT population**

Number of patients	Success rate (N, %)	95% C.I.
236	118 (50%)	(43%, 57%)

Source: [Appendix 12.1.9.2 Statistical Appendix 7.7](#)

In this analysis, 118 of 236 patients (50%) achieved sponsor-defined treatment success. Additionally, because questions regarding data quality for one investigator site (Dr. Nancy Olivieri, Toronto, Canada) were raised regarding one of the studies (LA-01) [see the 11/30/09 CR letter], an analysis was performed further excluding all data from that study and all data from the other study (LA-03) to which that investigator had contributed. For that analysis 109 of 220 (50%) patients achieved treatment success.

Finally, because the patients in the pediatric study (LA30-0307) were treated with a deferiprone solution that is not the subject of this NDA, an additional analysis was conducting excluding those patients as well as patients who had received combination/concurrent therapy. In that analysis 99/197 (50%) of patients achieved treatment success for the primary efficacy endpoint.

Results of the secondary efficacy analyses for change in liver iron concentration (LIC) and change in cardiac MRI T2\* are shown in the following tables.

**Table 7.4.1-8 Overall success rate for LIC – ITT population**

Study	Number of patients	Success rate (N, %)	95% C.I.
Overall	117	49 (42%)	(33%, 51%)

Source: [Appendix 12.1.9.2 Statistical Appendix 5.1](#)

**Table 7.4.1-11 Overall success rate for cardiac MRI T2\* – ITT population**

Study	Number of patients	Success rate (N, %)	95% C.I.
Overall	39	24 (62%)	(45%, 77%)

Source: [Appendix 12.1.9.2 Statistical Appendix 6.1](#)

The sponsor-defined success rate was 42% for LIC and 62% for cardiac MRI T2\*. The mean change in LIC was a decrease of 1.7 mg Fe/g dry weight and ranged from a decrease of 32.6 mg Fe/g dry weight to an increase of 14.5 mg Fe/g dry weight. The mean change in Cardiac MRI T2\* was an increase of 3.3 msec and ranged from a decrease of 2 msec to an increase of 12.7 msec.

It should be noted that while the populations for the primary and secondary efficacy analyses overlapped, the populations for the secondary efficacy analyses were not subsets of the primary efficacy population for change in serum ferritin. Among the patients enrolled in the study, 228 were evaluable for serum ferritin only, 68 were evaluable for LIC only, and 9 were evaluable for cardiac MRI T2\* only. Thirty-one (31) were evaluable for both serum ferritin and LIC, 12 for both serum ferritin and cardiac MRI T2\* and 25 for both LIC and cardiac MRI T2\*. Only 7 patients were included in the analysis populations for all three of the efficacy endpoints.

### **Safety Update**

The safety of deferiprone was reviewed in detail during the first review cycle for the NDA. Please refer to Dr. George Shashaty's Clinical Review (10/19/2009) and my Cross-Disciplinary Team Leader (CDTL) review (11/25/2009) of the first cycle NDA submission. For this resubmission no new patients have been treated in clinical trials and the sponsor has simply updated the safety database with additional post-European Union (EU) approval surveillance adverse event reporting data. The new data do not change the adverse event profile for deferiprone. The safety profile for the patients included in Study LA36-0310 was similar to that for the overall safety database. The most frequent adverse drug reactions were chromaturia, nausea, vomiting, and arthralgia.

The most important adverse drug reaction was agranulocytosis, which was seen in 1.7% of patients in the overall safety database and 1.3% (3) of patients in the LA36-0310 study. Neutropenia occurred in 5-10% of patients in the individual studies. In the post-EU approval surveillance experience there have been 94 reports of agranulocytosis including 13 deaths.

Among the 642 patients in the clinical trials safety database, during deferiprone treatment increased alanine aminotransferase was reported in 8.7% of patients and was considered possibly drug related in 7.5% of patients. Three patients experienced serious hepatobiliary events (cholelithiasis, hepatitis, hepatic congestion). Among the patients in the clinical trials 40.2% were positive for hepatitis C prior to deferiprone administration, 43.5% were negative and status was missing for 16.4%. The sponsor reported that 50 patients were known to have hepatic fibrosis at study entry. One patient ([2007AP000570], a patient  $\beta$ -thalassemia major and history of Hepatitis C and splenectomy), had progression after about 6 years on deferiprone, developed hepatocellular carcinoma, underwent liver transplant and subsequently died due to complications of cirrhosis. No new cases of hepatic fibrosis were reported in the clinical

studies. The sponsor reports that no cases of hepatic fibrosis have been reported among the 234 post-EU approval surveillance adverse event reports that have been received. Dr. Shashaty indicates in his 10/19/2009 Clinical Review that in the post-EU marketing experience drug-induced hepatitis associated with the administration of deferiprone was reported in 1 case with a positive-rechallenge. In clinical trials with deferiprone an elevation in liver enzymes occurred in 6% of treated patients at a rate of 3.7 per 100 patient years of exposure.

In the clinical studies there was one case of torsades de pointes, one case of seizure and one case of Henoch-Schönlein purpura.

Also, with regard to safety it should be noted that based on animal studies deferiprone is genotoxic and causes developmental toxicity (skeletal and soft tissue malformations in offspring of rats and rabbits). Dr. Shashaty's 10/19/2009 review reports that there have been 6 reports of pregnancy in persons receiving deferiprone. Deferiprone was discontinued between the 5<sup>th</sup> and 6<sup>th</sup> month of pregnancy in 3 patients (not known for other 3). Four pregnancies produced apparently healthy offspring at term, one pregnancy terminated spontaneously and outcome information was not available for the other case. Two pregnancies occurred in the partners of 2 patients with thalassemia treated with deferiprone. The offspring in one case had mild hypospadias and the other had normal growth and development.

### **Reviewer's Comments and Discussion**

Efficacy: The sponsor has conducted an analysis (Study LA36-0310) of a subpopulation of patients drawn from its previously conducted studies and defined as being inadequately treated with current chelation therapy, based on having previously been treated with a chelator (mostly deferoxamine) prior to deferiprone and having serum ferritin 2500 µg/L, cardiac MRI T2\* < 20 msec and/or liver iron concentration (LIC) > 7 mg Fe/g dry weight. The vast majority (94.3%) of patients had β-thalassemia syndromes as the underlying disease. Important for the U.S. population, only 2 patients had sickle cell disease as the underlying disease. For patients in the analysis population who received deferiprone for up to one year and had baseline and follow-up data for serum ferritin (primary efficacy endpoint) 52% (136/264) had a 20% or greater decline in serum ferritin from baseline up to 1 year after starting deferiprone. Excluding patients who received concurrent other chelators and those from Dr. Olivieri's site where there were questions of data quality, 50% (109/220) of patients met the primary efficacy endpoint for success. For the secondary endpoints the sponsor-defined success rate was 42% for LIC and 62% for cardiac MRI T2\*.

As stated by Dr. Shashaty in his Clinical Review (9/16/2011), "The sponsor has met its benchmarks for the primary efficacy endpoint for Study LA36-0310." Nevertheless, there are some limitations in the design of the study. These include: that the study was single-arm and non-randomized; data were pooled from heterogeneous studies that differed in deferiprone doses, treatment duration, objectives, and other aspects; for most

patients there was limited information available on prior therapies including specific drug, doses, times and duration of treatment, and compliance. There also are issues with regard to the interpretation of the study results. These include: that the change in serum ferritin is a non-specific endpoint and at best a surrogate for clinical improvement with removal of iron from the body; change in LIC was available for only 117 patients and showed the weakest efficacy results (42% of patients with sponsor-defined success); change in cardiac MRI T2\* was small and data to show quantitative relationship between the amount of change in cardiac MRI T2\* and cardiac function is lacking. Also, there was limited information on duration of responses and exploration of dose-response relationship was limited.

Regarding interpretation of the LA36-0310 study results, the FDA Statistical Review of the application (Qing Xu, Ph.D., 9/16/2011) comments:

“The sponsor’s efficacy analysis for serum ferritin by pooling 12 studies showed that the overall success rate was 52% with 95% CI of (45%, 58%). As the lower limit of the 95% CI is larger than 20%, the protocol defined endpoint was met for this trial. However, this study has several serious limitations including lack of randomization, lack of control group, high rate of missing data and ignoring the variation between studies by simple pooling, all of which can introduce biases to the primary outcome. Therefore, it is unclear whether the efficacy shown in the study is solely due to the Ferriprox therapy, and the interpretation of these analysis results should be taken cautiously.”

Safety: The safety profile of deferiprone in the current resubmission is unchanged from that reflected in the original submission. Agranulocytosis remains the major concern. Regarding agranulocytosis, in his Clinical Review (9/16/2011) Dr. Shashaty comments, “The clinically most important adverse reaction associated with the use of deferiprone continues to be the development of agranulocytosis. This adverse reaction occurred in 1.7% of patients treated with the drug in clinical trials. It appears to be more common in patients with non-thalassemic disorders than in patients with thalassemia, perhaps because in the latter there is often a deficiency of bone marrow production and these patients may be more susceptible to an additional marrow insult caused by deferiprone. The development of neutropenia may be a herald of progression to agranulocytosis, but this is not clear. In patients who survive the episode of agranulocytosis, thus far no apparent permanent bone marrow incapacitation has been observed.”

Deferiprone appears to be able to cause hepatotoxicity (elevation of hepatic transaminases). Long-term hepatic sequelae are not clear and may be difficult to evaluate because of confounding due to high rates of underlying history of hepatitis C infection and natural history of disease in the population treated.

Deferiprone is genotoxic and causes developmental toxicity and the labeling should reflect this risk.

There was one case of torsades de pointes. A thorough QT study has not yet been conducted for deferiprone.

### **Benefit/Risk and Recommendations**

Clinical review of the application finds that based on the available information in the NDA application, deferiprone treatment appears to significantly decrease serum ferritin, a commonly used parameter for following body iron burden in patients undergoing chronic red blood cell transfusions, in about 50% of patients who have been assessed as being inadequately treated with other iron chelators. The safety profile for this “second-line” use appears similar to that for the overall population of patients who have received deferiprone. Also, this NDA for deferiprone was presented to a meeting of the Oncology Drugs Advisory Committee on September 14, 2011. Considering the available information, the Committee concluded with a 10 yes to 2 no vote that there was a favorable benefit/risk profile for deferiprone in the treatment of patients in whom current chelation therapy is inadequate.

The primary Clinical Review (Dr. George Shashaty, 9/16/2011) recommends that:

“Deferiprone should not be approved for “the treatment of patients with transfusional iron overload when current chelation therapy is inadequate”.

However, if the sponsor agrees to change the indication to “the treatment of patients with thalassemia with transfusional iron overload when previous chelation therapy with other approved iron chelators has been unsuccessful”, deferiprone should receive Accelerated Approval under the requirements of 21CFR314.500-314.560 (Subpart H- Accelerated Approval of New Drugs for Serious of Life-Threatening Illnesses).”

I concur with Dr. Shashaty’s recommendation for approval of deferiprone under Subpart H for a revised indication for treatment of transfusional iron overload in thalassemia patients in whom prior treatment with other chelators has proven inadequate.

Unfortunately, at present there are no data to support expanding the indication to populations other than thalassemia. For the U.S. population, patients with thalassemia are likely to constitute a minority of those who might potentially be exposed to deferiprone. Based on Dr. Shashaty’s 3/18/2011 review of the Periodic Safety Update Report (PSUR) for Exjade (deferiasirox) (NDA 21882), approved for the indication “for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older”, patients with thalassemia accounted for approximately 10 – 11%, myelodysplastic syndrome for approximately 20 – 42%, sickle cell diseases (SCD) for approximately 18 – 39%, other forms of anemia for approximately 18 – 22% and unknown diseases for approximately 8 – 10% of the total use of deferiasirox. It is not unlikely that once deferiprone enters the U.S. market patients with SCD may be the largest population actually using the drug. Therefore, it should be required as a condition of approval that the sponsor conduct a post-marketing clinical study to evaluate efficacy and safety of deferiprone in patients with SCD.

Other considerations for post-marketing study requirements should include the following:

- Because changes in serum ferritin are at best a surrogate for clinical benefit of chelation therapy in transfusional iron overload, the sponsor should conduct a study to evaluate effect of deferiprone on survival or important morbidity (such as cardiac dysfunction) in treated patients.
- Because deferiprone will be a life-long treatment for patients and currently experience with long-term use is limited, a registry should be established to follow patients long-term for evidence of hepatic toxicity (particularly fibrosis), development of cancer, and evidence of long-term clinical benefit.
- The sponsor should perform a thorough QT study.
- Evaluation of deferiprone use in pediatric patients with  $\beta$ -thalassemia should be encouraged.

See Dr. Shashaty's 9/16/2011 Clinical Review for additional recommendations for further studies and labeling recommendations. Final wording of the labeling should be negotiated with the sponsor.

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/s/  
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KATHY M ROBIE SUH  
09/27/2011

## CLINICAL REVIEW

Application Type NDA  
Application Number(s) 21825  
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Reviewer Name(s) George Shashaty  
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Established Name Deferiprone  
(Proposed) Trade Name Ferriprox  
Therapeutic Class Iron Chelator  
Applicant ApoPharma

Formulation(s) Tablet  
Dosing Regimen 25-33 mg/kg three times daily  
Indication(s) Transfusion-related hemosiderosis  
Intended Population(s) Thalassemia

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## **1 Recommendations/Risk Benefit Assessment**

See Pages 7-11, Section 1 of previous review in Appendix 9.4.

### **1.1 Recommendation on Regulatory Action**

Deferiprone should not be approved for “the treatment of patients with transfusional iron overload when current chelation therapy is inadequate”. However, if the sponsor agrees to change the indication to “the treatment of patients with thalassemia with transfusional iron overload when previous chelation therapy with other approved iron chelators has been unsuccessful”, deferiprone should receive Accelerated Approval under the requirements of 21CFR314.500-314.560 (Subpart H- Accelerated Approval of New Drugs for Serious of Life-Threatening Illnesses).

This recommendation is made on the basis of the sponsor’s submission of the analysis from study LA36-0310 and data from supporting studies, virtually all of which were submitted in the original NDA dated January 29, 2009. After the Agency sent the sponsor a Complete Response letter to the original application, and in consultations between the sponsor and the Agency, an agreement was reached that, if the sponsor decided not to perform adequate and well controlled trials to determine the efficacy and safety of the use of deferiprone for the indication sought, the sponsor could seek an approval for second/third line treatment for deferiprone if the sponsor would analyze data already available within its database to determine the efficacy and safety of deferiprone in patients who had not been successfully treated with other available iron chelators. The sponsor indicated that the only endpoint that was common to all of its studies was the measurement of the serum ferritin. Although the effect of deferiprone on changes in serum ferritin was not considered the optimal endpoint for analysis, the Agency agreed that it would review such an analysis to determine whether or not the analysis would provide data to support the efficacy and safety of deferiprone that might lead to the approval of the drug.

Study LA36-0310 assessed the change in serum ferritin from baseline to the end of one year’s treatment with deferiprone in patients (almost all with thalassemia) with transfusion related hemosiderosis who appeared to be unsuccessfully treated with other chelators (almost exclusively deferoxamine). Patients were considered to be unsuccessfully chelated if, despite the use of a chelator, they continued to have a serum ferritin in excess of 2,500 µg/L prior to the initiation of deferiprone therapy. Secondary endpoints analyzed included changes in cardiac magnetic resonance imaging (MRI) T2\* in patients with a baseline MRI T2\* of less than 20 msec, and changes in liver iron concentration (LIC) in patients with a baseline LIC of greater than 7 mg Fe/g dry weight (dw). These latter values were also considered to be consistent with unsuccessful treatment with an iron chelator.

The patients were selected for inclusion in the Study LA36-0310 by an independent committee based on a review of all patients who had been previously enrolled in sponsor-supported studies, almost all of which had been submitted to the original NDA. The committee selected patients for possible inclusion based on a pre-specified protocol. Inclusion required that the patient must have been receiving iron chelating therapy and that, despite such therapy, continued to have one or more measurements indicating a persistently elevated body iron burden as described above. All patients were screened from data provided by the sponsor and available in its database from previous trials. The independent committee had no knowledge of the outcomes of deferiprone treatment. After receiving the list of potential enrollees for the study from the independent committee, the sponsor's statistics facility examined the same database for patients who had had at least one post-baseline measurement of any of the primary or secondary endpoint assessments within one year of commencing treatment with deferiprone. These patients were then enrolled and analyzed for the primary and secondary endpoints. Success was defined as a decrease in serum ferritin of 20% or more, a decrease in LIC of 20% or more or an increase in MRI T2\* of 20% or more.

Seven hundred forty seven (747) subjects were evaluated by the independent committee for possible enrollment. Of these, 264 met the inclusion criteria for serum ferritin, 117 for LIC and 39 for MRI T2\* based on a review of the sponsor's database. The overall success rate for the serum ferritin endpoint was 52% (C.I., 45%, 58%), while those for the LIC and MRI T2\* were 42% (C.I., 33%, 51%) and 62% (C.I., 45%, 77%), respectively. Various subset analyses were consistent with analyses for the primary and secondary endpoints.

No safety data were analyzed in study LA36-0310 since these data had previously been submitted with the original NDA. However, a safety update with re-integration of safety information was submitted with the resubmission. Data from the safety update did not change the conclusions of the safety evaluation.

Contributing to the decision regarding approvability were the change in the indication statement and the data that were submitted with the original NDA (please refer to previous review dated October 19, 2009 in Appendix 9.4).

## **1.2 Risk Benefit Assessment**

Patients with transfusional hemosiderosis treated with either deferoxamine or deferasirox may have an inadequate reduction in total body iron burden. Reasons for this include the difficulty of administration leading to suboptimal compliance, intolerance to drug-induced symptoms (particularly gastrointestinal and dermatological), the development of adverse reactions that lead to dose modifications or withdrawal, or unexplained causes that limit the iron excretion effects of the currently approved iron chelators. For such patients, there are no alternative therapies and, since many of them have a continuing

requirement for transfusion therapy, iron overloading progresses, eventually leading to organ dysfunction and, possibly, death. The organ most commonly compromised, and which is the most common cause of death (at least in persons with thalassemia), is the heart. Cardiac failure and arrhythmias are responsible for approximately 70% of deaths in patients with thalassemia (Borgna-Pignatti C et al 2004. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica* 89:1187-93).

Therefore, an additional iron chelator would be of utility for such patients, even if there are risks associated with its administration. For deferiprone, whose most important adverse reaction is the development of agranulocytosis (approximately 1.7% of users), because of the lack of alternative drugs, the risks of deferiprone might be acceptable to gain its benefits in persons with thalassemia.

I believe that the indication for the use of deferiprone should be restricted to patients with thalassemia. Approximately 95% of all of the patients in whom the drug was studied had thalassemia as the anemia that led to the requirement for chronic transfusion therapy. There have only been a total of 35 patients with sickle cell disease, myelodysplastic syndrome (MDS) with variants, and other transfusion dependent anemias who have been treated with deferiprone in the clinical studies. All of the non-thalassemic patients were enrolled in a Compassionate Use Treatment protocol (LA-04) and the interpretation of the data from that study is complicated by the multiplicity of physicians involved, variability in inclusion/exclusion criteria, the adequacy of data regarding efficacy, compliance and safety assessments and the use of concomitant chelators in a number of the enrollees.

In addition, although I believe that there is adequate information from the literature and from medical experience regarding the clinical benefits of iron chelation therapy on mortality and morbidity in patients with thalassemia, there are no such data available for patients with other hemoglobinopathies or other diseases in which chronic transfusions may be required, such as MDS and variants. Since most such patients are older and have a lesser lifetime transfusion burden compared to patients with thalassemia, do not appear to have a markedly increased frequency of organ dysfunction due to iron overload, often die from concomitant diseases before hemosiderosis causes clinical symptomatology and have a disordered bone marrow that may make them more liable to the development of agranulocytosis, deferiprone should not be labeled with an indication for these patients (who in the United States are probably the largest population to whom it would be marketed). Approval for the indication for deferiprone in patients with non-thalassemic hemoglobinopathies and MDS and related diseases should be considered only after adequate and well-controlled studies are performed from which analyses are provided that demonstrate the efficacy and safety of deferiprone in those populations.

### **1.3 Recommendations for Postmarket Risk Management Activities**

Because deferiprone has been approved in many countries, in some for more than 10 years, the safety profile is reasonably known. As noted, agranulocytosis is the clinically most important adverse reaction associated with the drug. Because of this risk, all patients who receive the drug must have an absolute neutrophil count performed prior to commencing therapy with deferiprone followed by weekly determination of the absolute neutrophil count while continuing to receive the drug.

### **1.4 Recommendations for Postmarket Studies/Clinical Trials**

The following studies should be required.

- A registry of patients with thalassemia and transfusion related hemosiderosis who cannot be effectively treated with either deferoxamine or deferasirox with data accumulated for a time span sufficient in length to determine the natural history and the efficacy and safety of the use of deferiprone in these individuals. The registry should focus on mortality and morbidity in patients receiving deferiprone, hepatic function, the development of malignancies and persistence of drug effect on body iron load.
- A prospective randomized trial in patients with thalassemia and transfusion related hemosiderosis who cannot be effectively treated with deferoxamine comparing the efficacy and safety of the use of deferasirox with the efficacy and safety of the use of deferiprone in that population. An alternative acceptable trial in a similar population would compare the use of deferasirox alone with the combination of deferasirox and deferiprone.
- Pharmacokinetic and pharmacodynamic studies in subjects with varying degrees of hepatic and renal dysfunction.
- A study in humans to determine the effects of deferiprone on the QT interval of the heart.
- A dose-response study in persons with thalassemia and transfusional hemosiderosis to determine the optimal and maximal doses for deferiprone.
- At this time, recommendations from the Pediatric and Maternal Health Staff, OND have not been finalized. Depending on further discussions, there is the possibility that a study of the efficacy and safety of the use of deferiprone in pediatric patients may be required.

## **2 Introduction and Regulatory Background**

## **2.1 Product Information**

See Page 11, Section 2.1 of previous review in Appendix 9.4.

## **2.2 Currently Available Treatments for Proposed Indications**

See Page 12, Section 2.2 of previous review in Appendix 9.4

## **2.3 Availability of Proposed Active Ingredient in the United States**

The active ingredient is not currently available in the United States.

## **2.4 Important Safety Issues with Consideration to Related Drugs**

See Page 12, Section 2.4 of previous review in Appendix 9.4.

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

See Pages 12-17, Section 2.5 of previous review in Appendix 9.4.

The original NDA for deferiprone was submitted on January 29, 2009. Subsequent to a review of the data from the initial submission, a Complete Response letter was sent to the sponsor on November 30, 2009 indicating that deferiprone was not approved and providing the reasons for that decision (see Appendix 9.5). A summary of the deficiencies enumerated in the Complete Response letter included these problems within the original submission:

1. The submission lacked substantial evidence for efficacy and safety from adequate and well-controlled trials.
2. The primary efficacy endpoint of the single major controlled trial submitted by the sponsor was the change in cardiac MRI T2\* which was said to measure iron content within the heart. FDA stated that this endpoint was a surrogate endpoint and there were no data to support the incremental changes in the values as predictive of clinical benefit.
3. The efficacy and safety of the use of deferiprone in the treatment of transfusional hemosiderosis in pediatric patients, a likely target population, were not adequately studied.
4. Long term studies of the continued efficacy and safety of deferiprone for extended periods had not been adequately performed. This was important in view of the fact that for the target population, the likelihood of the need for lifelong therapy was probable.

5. FDA requested a more thorough assessment of the arrhythmogenic potential of deferiprone, particularly for deferiprone's effect on QT prolongation as there was one patient in the clinical trials who had had an episode of torsade de pointes.
6. FDA inspectional findings could not fully verify the accuracy of data submitted by the sponsor for Study LA-01 (a randomized, controlled trial).
7. In the submitted trial, changes in serum ferritin and liver iron concentration, measures that have typically been used to determine the efficacy of a chelator, were not well correlated with the changes in cardiac MRI T2\*.
8. In the submitted trial, there was a higher frequency of hepatic transaminase elevations in patients randomized to deferiprone compared to patients randomized to deferoxamine. This was of concern because of hepatic adverse reactions reported by early investigators of deferiprone.
9. Supporting studies submitted by the sponsor suffered from various important deficiencies and could not add sufficient support to approve the application.
10. The frequency of the development of drug-induced agranulocytosis was approximately 1.7% of all patients who received deferiprone in clinical trials. Death due to agranulocytosis with infection had been documented in 13 patients in postmarketing reports and these occurred in an unpredictable fashion.
11. FDA stated that complete and accurate data from Study LA-01 was of great interest because of its design, size and endpoint, and that the inability to verify the data in the trial was problematic.
12. Published literature did not consistently support the efficacy and/or safety of the use of deferiprone for the indication sought.

Following the issuance of the Complete Response letter, there were several interactions (face-to-face, teleconference, letters) between the sponsor and FDA. As a result of these interactions, the following ensued:

1. As suggested by FDA, the sponsor revised the proposed indication from “(1) for the treatment of iron overload in patients with transfusion-dependent thalassemia, and (2) for the treatment of iron overload associated with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate” to “for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate”.
2. Although FDA recommended that the sponsor provide data from adequate and well-controlled trials to support the application for the approval of deferiprone, the sponsor declined to do so, stating that it believed that there was sufficient clinical experience with the drug from more than a decade of use in a number of countries throughout the world in which deferiprone had already been approved.
3. The sponsor informed FDA that it would perform a new analysis (study LA36-0310) based on pre-existing data to provide evidence for the value of the use of deferiprone in patients with transfusion-induced hemosiderosis who were unable to be successfully treated with other approved iron chelating agents. The primary efficacy endpoint of the analysis was to be the change in serum ferritin from

baseline to the end of 1 year of treatment with deferiprone, and secondary endpoints of changes in liver iron concentration (LIC) and cardiac MRI T2\* amongst the available populations. FDA indicated that it would be willing to review such analyses but cautioned that there would be difficulty in determining the benefit/risk assessment based on these data.

On April 13, 2011, the sponsor submitted its response to the Complete Response letter. In this submission were included:

- Cover letter
- Responses to all Clinical Questions listed in the Complete Response letter
- Responses to all Clinical Pharmacology Questions in the Complete Response letter
- Response to an FDA Facility Inspections deficiency statement
- Response to FDA Inspection Observations of Study LA-01
- Safety Update
- Proposed label for deferiprone
- Clinical study report for study LA36-0310 entitled “Analysis of Data from Clinical Studies of Ferriprox to Evaluate its Efficacy in Patients with Iron Overload for Whom Previous Chelation Therapy Has Been Inadequate”
- Multiple references pursuant to various other parts of the submission

The current submission was characterized by FDA as a Type 2 resubmission with timelines assigned accordingly.

The **Cover Letter** stated that the sponsor believed that it had addressed all of the issues raised in the FDA’s Complete Response letter. The sponsor accepted the advice of the Division that deferiprone be re-positioned from first line to second/third line therapy for the indication. The sponsor referred to the submitted study (LA36-0310) which it said demonstrated that deferiprone had achieved success in its goal of lowering serum ferritin by more than 20% in more than 20% of treated patients (see Efficacy Review below). The sponsor stated that it was hampered in its ability to provide a response to allegations of inaccurate data collection and analyses because FDA did not reveal the entire inspection report submitted by the Division of Scientific Investigation. The sponsor stated that the cancelation of the original Advisory Committee was unwarranted and requested that the review of the application for the NDA be expedited. The sponsor stated that there were more than 36,000 patient-years of marketed exposure of patients to deferiprone outside the United States. The sponsor submitted recent published information that it stated supported the effectiveness of deferiprone in the prevention of clinical heart disease and other organ dysfunction in patients with hemosiderosis.

In its **Responses to all Clinical Questions in the Complete Response** letter, the sponsor re-iterated its belief that the data from its clinical trials and post-marketing experience

were more than adequate to demonstrate the clinical value of deferiprone for the indication. Additionally, the sponsor stated that study LA16-0102 was an adequate, well-controlled trial that had documented the superiority of the use of deferiprone compared to deferoxamine in its beneficial effects on iron deposition in the heart, reflected as a 3.7 msec mean increase in cardiac MRI T2\* value. The sponsor provided no additional data that showed that an increase in cardiac MRI T2\* predicted a clinical benefit in patients with cardiac siderosis. No data from an adequate QTc study were submitted, and the sponsor stated that there were no data in its safety database that indicated that QT prolongation occurred in association with the administration of deferiprone. The sponsor continued to be unable to provide source documents from study LA-01 because the primary investigator would not make them available; however, the sponsor did provide tables for patients who were said to have been inappropriately excluded or included in the analysis sets. In regard to hepatic functional abnormalities, the sponsor indicated that no episodes of liver failure have been reported during the past 24 years during which deferiprone has been available for investigation and marketing with an estimated drug exposure of more than 34,000 patient-years. The sponsor referred to numerous clinical publications that relate various authors' experience with deferiprone.

In its **Responses to all Clinical Pharmacology Questions in the Complete Response** letter, the sponsor stated that the number of potential patients with hepatic or renal impairment and expected to be treated with deferiprone is very small and does not warrant formal studies with deferiprone in patients with hepatic or renal dysfunction, that patients with hepatic or renal dysfunction can be managed using recommendations in the label, or studies in such persons can be performed after drug approval. Additionally, deferiprone is metabolized almost exclusively via UGT 1A6 (glucuronosyltransferase) which metabolizes only a small number of drugs, and this makes a study of the effect of inhibition and induction of UGT 1A6 on the metabolism of deferiprone unnecessary.

In its **Response to an FDA Facility Inspections deficiency statement**, the sponsor stated that it is "well on its way to executing and implementing.....processes and practices that will satisfactorily address all FDA regulatory concerns". (Please refer to CMC review for current status of manufacturing facilities).

In its **Response to LA-01 FDA Inspection Observations**, the sponsor reviewed the FDA Establishment Inspection Report (EIR) #FEI 300761479. The sponsor indicated that the inspection was unusual for the following:

1. Dr Olivieri (the principal investigator) refused to allow any member of ApoPharma, any representative from the Hospital for Sick Children (her home institution at the time of the study) or her co-investigator (Dr. Gideon Koren) to be present.
2. Dr. Olivieri was the sole source of information for the inspector.
3. Time limitation of the inspection.
4. Lack of access by inspector to source documents.

5. The sponsor's belief that much of the information presented to the inspector was incorrect or misrepresented.

Several areas of the inspection and its interpretation were commented upon by the sponsor as follows:

1. Dr. Olivieri's main concerns, which the sponsor indicated were not forwarded to it until after she had been terminated as an investigator (May 24, 1996) for reasons of non-compliance with the requirements of the study, were that deferiprone may have played a causal role in the development of hepatic fibrosis in treated patients and that the efficacy of iron excretion due to the drug declined over time. The sponsor had reported these concerns to FDA in annual reports of its IND in 1996-1998. The concerns appeared not to have been shared with other investigators participating in the study.
2. Panels established by the sponsor reviewed the data from the study (including review of available liver biopsies by a sponsor-appointed pathologist) and concluded that there was no evidence of progressive fibrosis in patients treated with deferiprone and that deferiprone continued to promote iron excretion indefinitely. Additionally, after 23 years of use in clinical trials and in post-marketing experience, progressive hepatic fibrosis has not arisen as an adverse reaction associated with the use of deferiprone.
3. The sponsor stated that an independent review of liver biopsies from another study (LA-02/06) commissioned by the sponsor failed to show progression in liver fibrosis in patients treated with deferiprone.
4. Dr. Olivieri informed ApoPharma that her review of data from study LA-03 indicated a loss of efficacy over time in several patients. The data for that review were subsequently forwarded to ApoPharma in a spreadsheet format. ApoPharma reported discrepancies between the spreadsheet and the case report forms to Dr. Olivieri who, in turn, provided a finalized dataset to ApoPharma. Review of these data by ApoPharma concluded that there was no loss of efficacy. ApoPharma organized an Expert Review Panel which reviewed all available data from both studies LA-01 and LA-03. This panel did not find evidence for loss of efficacy.
5. ApoPharma stated that there were significant problems with Dr. Olivieri regarding compliance with the protocol and data submission.
6. ApoPharma is uncertain as to which patients are included in the FDA inspector's verification of 45 liver biopsy pathology reports from 21 patients at the Hospital for Sick Children. ApoPharma cannot tell whether these patients were included in study LA-01 or LA-03. In a report from Dr. Olivieri to the FDA and to ApoPharma, there were reports of 66 fibrosis scores from 21 patients in study LA-03. ApoPharma stated that no liver fibrosis scores were submitted for patients treated on the deferoxamine arm in study LA-01.
7. The "Olivieri Report" referred to in the inspection as a source of "additional background information" was based on information provided by Dr. Olivieri and had no input from any of the other major persons involved with the events.

8. Although the inspection report states that Dr. Gary Brittenham performed all of the liver iron measurements, ApoPharma stated that Dr. D.M. Templeton of the University of Toronto performed some of them.
9. ApoPharma stated that it did not exclude data from 29/64 treated subjects from the main analysis as implied in the EIR. ApoPharma stated that 75 patients were enrolled in study LA-01, that it has provided data on the 71 of them that were submitted by Dr. Olivieri, and that the reasons for the exclusion of any data points were explained in the original submission. Some patients were excluded from the Per Protocol (PP) analysis. Reasons for exclusion from the PP analysis were absence of baseline measurement (5 patients), absence of follow-up measurements (21 patients) and non-completion of 24 months of therapy (6 patients). ApoPharma stated that the other 39 patients were then included in the PP analysis.
10. ApoPharma stated that the FDA inspector verified data in tables against data summaries maintained by the investigator, an assessment that is fraught with limitations. ApoPharma provided its objections to the FDA inspector's interpretation of discrepancies on pages 8 – 13 of the EIR (excluded patients, long-term efficacy data, length of treatment duration, protocol violations regarding the permissible length between assessment of LIC and commencement on deferiprone treatment, discrepancies between same patient LIC values reported by the FDA inspector and ApoPharma [whose values were said to have been taken from case report forms submitted by Dr. Olivieri], omission of patients with favorable effects from administration of deferoxamine and of patients with unfavorable effects from administration of deferoxamine).
11. Dr Olivieri stated that one patient was reported by ApoPharma to have developed neutropenia but could more accurately be described as having developed agranulocytosis. ApoPharma points to its NDA submission in which the patient was reported as having had agranulocytosis.
12. ApoPharma stated that, contrary to the FDA inspector's assessment, patient eligibility and assessments were not compliant with requirements of the study (some informed consents were obtained after, rather than before, enrollment; baseline assessments occurred earlier than permissible; incorrect stratification; untimely assessments).

In support of these statements, ApoPharma provided copies of a number of documents that are attached as Appendices to its statements.

## **2.6 Other Relevant Background Information**

See Page 17, Section 2.6 of previous review in Appendix 9.4.

### **3 Ethics and Good Clinical Practices**

See Page 18, Section 3 of previous review in Appendix 9.4

#### **3.1 Submission Quality and Integrity**

See Page 18, Section 3 of previous review in Appendix 9.4

#### **3.2 Compliance with Good Clinical Practices**

See Page 18, Section 3 of previous review in Appendix 9.4

#### **3.3 Financial Disclosures**

See Page 18, Section 3 of previous review in Appendix 9.4. The sponsor has submitted a statement signed by both members of the Independent Party that was responsible for the selection of potential enrollees into Study LA36-0310 that there was no financial benefit that would accrue to either of them based on the results of the study.

### **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

#### **4.1 Chemistry Manufacturing and Controls**

See Page 19, Section 4.1 of previous review in Appendix 9.4

#### **4.2 Clinical Microbiology**

See Page 19, Section 4.2 of previous review in Appendix 9.4

#### **4.3 Preclinical Pharmacology/Toxicology**

See Page 19, Section 4.3 of previous review in Appendix 9.4

#### **4.4 Clinical Pharmacology**

See Page 19, Section 4.4 of previous review in Appendix 9.4

##### **4.4.1 Mechanism of Action**

See Page 19, Section 4.4.1 of previous review in Appendix 9.4

##### **4.4.2 Pharmacodynamics**

See Page 19, Section 4.4.2 of previous review in Appendix 9.4

##### **4.4.3 Pharmacokinetics**

See Page 20, Section 4.4.3 of previous review in Appendix 9.4

### **5 Sources of Clinical Data**

In the original NDA submission, the sponsor submitted data from studies that had been performed under its own auspices, as well as from studies that had been performed by other investigators and for which the sponsor did not have possession of, or access to, source data. These studies are referenced in the review of the original submission and are located on Pages 20-24, Section 5.1 of previous review in Appendix 9.4. Subsequent to the original submission of the NDA, the sponsor submitted the complete study report from Study LA30-0307 to IND 45724 on May 21, 2009.

In the current resubmission, the sponsor has submitted data from a single study (LA36-0310) entitled “Analysis of Data from Clinical Studies of Ferriprox to Evaluate its Efficacy in Patients with Iron Overload for Whom Previous Chelation Therapy Has Been Inadequate” in support of the proposed indication. In this analysis, the sponsor reviewed data from previously performed studies of the use of deferiprone in patients with transfusional iron overload, virtually all in patients with thalassemia, who were defined as inadequately treated (based on specified measurements of serum ferritin, LIC or cardiac MRI T2\*) to determine the effects of the drug on these measurements after one year of treatment. The trials from which the patients were selected were a subset of the studies referred to in the previous paragraph.

## 5.1 Tables of Studies/Clinical Trials

The submission is based on a single study as shown in the table below.

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A tabular listing for LA36-0310, presented in Module 5 of NDA 21-825 with the response to the Complete Response Letter.

Type of study	Study identifier/ Study Title	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s), Dosage regimen, Route of administration	No. of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Efficacy	LA36-0310: Analysis of Data from Clinical Studies of Ferriprox to Evaluate its Efficacy in Patients with Iron Overload for Whom Previous Chelation Therapy Has Been Inadequate	Module 5.3.3.4	The objective of this study was to evaluate the efficacy of oral administration of Ferriprox in the treatment of iron overload in patients in whom previous chelation had failed. The main criterion for chelation failure was defined as a baseline serum ferritin of $\geq 2,500$ $\mu\text{g/L}$ prior to the initiation of Ferriprox therapy. Secondary analyses were conducted on patients who showed evidence of a failed response to previous chelation therapy, as defined by: (1) excess cardiac iron stores as demonstrated by a cardiac MRI T2* $\leq 20$ ms; or (2) LIC of $\geq 7$ mg/g dry weight. <i>Primary endpoint:</i> Change from baseline in serum ferritin. <i>Secondary endpoint:</i> Change from baseline in cardiac MRI T2* and change from baseline in LIC.	Open label, uncontrolled retrospective analysis of pre-existing clinical data	Test product: Ferriprox® at a dose of 35 to 100 mg/kg/day, administered orally in either tablet or solution form.	747	Patients from existing clinical studies of Ferriprox with iron overload for whom previous chelation therapy has been inadequate	Up to 12 months	Completed; Full

MRI = Magnetic Resonance Imaging LIC = Liver iron concentration

## 5.2 Review Strategy

The results of a single study were included in this submission. For studies submitted in the original submission, see Pages 20-24 in Appendix 9.4. The current review focused on the results of the analysis performed in Study LA36-0310. This study analyzed only efficacy data and no safety analyses were performed. In addition, the sponsor also provided a current safety update and that was reviewed.

## 5.3 Discussion of Individual Studies/Clinical Trials

For studies submitted in the original submission, see Pages 20-24 in Appendix 9.4.

A single analysis (Study LA36-0310) was included in this submission.

## 6 Review of Efficacy

### Efficacy Summary

Based on the sponsor's trial, it can be concluded that the administration of deferiprone for 1 year at a dose of 75-100 mg/kg/d in 3 divided doses over the course of the day is

capable of inducing a fall in serum ferritin from baseline to the end of 1 year of therapy by > 20% in > 20% of patients who have not previously been successfully treated with other approved chelating agents. This lack of success with previous chelator therapy may have been occasioned by the inability of the previous chelator to cause a sufficient excretion of iron (treatment refractoriness) or was due to the development of adverse reactions to the drugs that could not be tolerated by the patient. The overwhelming majority of patients enrolled in the study had an underlying diagnosis of thalassemia that led to the need for chronic transfusion therapy. There were too few patients with non-thalassemic syndromes enrolled in the study to determine the efficacy of deferiprone for the treatment of transfusion-induced hemosiderosis in those populations.

## 6.1 Indication

The indication being sought is for:

“Ferriprox® (deferiprone) is an iron chelator indicated for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate”

### 6.1.1 Methods

Study LA36-0310 was designed as an analysis of existing data from studies previously conducted to evaluate the efficacy and safety of deferiprone in patients with transfusion related hemosiderosis (see Pages 20-24 of Appendix 9.4 for a table of these studies). The study was initiated after discussions between the sponsor and the Agency after the Agency had issued its Complete Response to the sponsor’s first NDA submission. In view of the fact that the Agency indicated in the Complete Response that the sponsor would have to perform additional trials to provide evidence for the efficacy and safety of deferiprone in patients with transfusion related hemosiderosis and the sponsor believed that additional trials would not be performed, the sponsor proposed an approach forward in which a revised indication as stated above would be pursued. Therefore, LA36-0310 was formulated to analyze the effect of deferiprone for its efficacy on transfusion related hemosiderosis in patients who had previously been unsuccessfully treated (failed) with another iron chelating agent.

The primary objective of the study was to evaluate the efficacy of oral administration of deferiprone in the treatment of iron overload in patients in whom previous chelation had failed. Failure of previous chelation to qualify for enrollment in Study LA36-0310 was defined by specific measures of serum iron, liver iron concentration or cardiac MRI T2\*.

The primary efficacy endpoint was defined as the change in serum ferritin from baseline to completion of up to one year of therapy. Secondary endpoints were defined as the change from baseline in MRI T2\* and LIC to completion of up to one year of therapy.

Patients enrolled in the trial were selected from studies previously submitted to FDA in support of the original NDA. An integrated dataset including all serum ferritin, LIC, and cardiac MRI T2\*, and data for demographics, disposition, medical history, exposure, and accompanied CDISC metatables created by Clinical Data Management at ApoPharma from these studies were sent to an Independent Party that was responsible for selecting patients for the analysis based on an Independent Party Charter. The Independent Party had no access to further chelator therapy administered or to the outcomes of any of the patients. The Independent Party consisted of two individuals:

- Ron Keren, M.D., Associate Professor of Pediatrics and Epidemiology, University of Pennsylvania School of Medicine
- Xianqun Luan, M.S., Biostatistician, Children's Hospital of Philadelphia

In the Independent Party Charter, the sponsor stated that the members of the Independent Party cannot have any financial, scientific or regulatory conflicts of interest, and has provided a statement to that effect signed by both members.

Patients eligible to be enrolled in the study were selected by the Independent Party based on pre-specified inclusion criteria including measurements of serum ferritin, LIC and cardiac MRI T2\* and previous treatment with an iron chelator. The two Independent Party members assembled patient cohorts independently using SAS programming and by following the Data Extraction Plan and the QC Plan. For each pair of cohorts, the selected patients were matched and compared for discrepancies. A QC log was issued and discrepancies were resolved before the final patient cohort lists were delivered to the sponsor. The signed QC log was delivered to the sponsor with the final selected eligible patient cohort lists.

Patients selected by the sponsor for enrollment in Study LA36-0310 from the eligible list provided by the Independent Party had to meet the following inclusion criteria:

- At least a single baseline value for serum ferritin, LIC or MRI T2\* available
- Follow-up assessment of serum ferritin, LIC or MRI T2\* after initiation of deferiprone and within one year of therapy
- Had been receiving standard iron chelation therapy with either deferoxamine or deferasirox and before receiving deferiprone had one or more of the following:
  - Serum ferritin > 2,500 µg/L
  - Cardiac MRI T2\* < 20 ms
  - LIC > 7 mg/g dry weight
- Treatment with deferiprone

Patients were excluded from enrollment for the following:

- Naïve to iron chelation therapy
- Never received deferiprone
- No data on serum ferritin, LIC or MRI T2\* either while receiving standard chelation therapy or after initiation of deferiprone, or both

- Had had an improvement in any of the measures of iron burden of  $\geq 20\%$  related to chelator therapy within the year prior to consideration for enrollment

Treatment with deferiprone in the great majority of patients consisted of the oral administration of deferiprone tablets at a dose of 75 mg/kg/d (in 3 divided doses) although some patients received higher or lower doses. In Study LA16-0102, the dose of deferiprone was 100 mg/kg/d for most of the trial.

The primary efficacy endpoint was the change in serum ferritin concentration from baseline to within one year of deferiprone therapy (defined as the observation closest to one year in a period of 15 months or at  $12 \pm 3$  months). For patients who stopped study treatment prior to one year, data collected up to 3 months after discontinuation was included and the value closest to the stopping date was used as the final result. Patients were considered to have been successfully treated if there was a decline in serum ferritin of at least 20% over that time period and the trial would be deemed to show evidence of efficacy if at least 20% of patients achieved the described efficacy endpoint.

Secondary endpoints included changes in the LIC and cardiac MRI T2\* over the same time period.

The definition of successful chelation therapy is shown in the following table.

**Table 5.5.3-1: Definition of Successful Chelation Therapy**

Primary endpoint	
• Based on Serum Ferritin	
Serum Ferritin at Baseline	Success
>2,500 $\mu\text{g/L}$	A $\geq 20\%$ decline in serum ferritin from baseline within 1 year of Ferriprox therapy.
Secondary endpoints	
• Based on Liver Iron Concentration (LIC)	
LIC at baseline	Success
>7 mg Fe/g dw	A $\geq 20\%$ decline in LIC from baseline within 1 year of Ferriprox therapy
• Based on Cardiac Iron Concentration (as assessed by MRI T2*)	
MRI T2* at baseline	Success
<20 ms	A $\geq 20\%$ increase in MRI T2* from baseline within 1 year of Ferriprox therapy

dw = dry weight; LIC = liver iron concentration

The Intent-To-Treat (ITT) population was the primary population for the efficacy analysis. This population comprised those patients that had taken at least one dose of deferiprone and had at least one post-baseline measurement of an efficacy variable. Data

were available from both randomized and non-randomized trials. The Per-Protocol (PP) population was the secondary population. This population comprised those patients that had completed their study of origin or at least one year of deferiprone therapy and had no missing data for the end of study measurement or the last scheduled measurement at the end of the first year for the efficacy measurement.

Serum ferritin was the primary efficacy endpoint, and LIC and cardiac MRI T2\* were secondary endpoints. The end of study value for all endpoints was that assessment that was obtained at the end of the trial (if less than 1 year) or the value obtained at 12 months or within 3 months thereafter, utilizing the value that was closest to the 12 month date. For subjects that stopped the study early, the value closest to the stopping date was the value used. Success was defined as noted in the table above. Success rates by study and overall and its 95% CI were calculated based on Clopper-Pearson exact confidence interval.

Trend analyses were performed for serum ferritin, LIC and cardiac MRI T2\* at different time points including those beyond 1 year.

The imputation method for missing data was the use of the Last Observation Carried Forward (LOCF).

Subgroup analyses were performed on the following:

- Subjects with one baseline determination for ferritin compared to those with multiple baseline determinations
- Subjects treated with another chelating agent who had a decline in serum ferritin of  $\geq 20\%$  in the year prior to treatment with deferiprone compared to the decline in serum ferritin of  $\geq 20\%$  during the year of deferiprone use
- Pediatric versus adult subjects
- Male versus female subjects
- Thalassemia versus non-thalassemia subjects
- Results in European versus non-European countries

An unplanned subgroup analysis was performed by excluding patients from Studies LA-08, LA-04 and LA-12-9907 who had had concomitant or combination therapy with another chelator (mostly deferoxamine) in order to determine treatment success for monotherapy with deferiprone.

### 6.1.2 Subject Disposition

A total of 746 patients with serum ferritin, LIC and/or MRI T2\* data were analyzed by the Independent Committee for study eligibility. Of these, 264 were eligible for the

serum ferritin criterion, 117 were eligible for the LIC criterion and 39 were eligible for the cardiac MRI T2\* criterion. These data are shown in the following tables.

**Table 6.1-1: Number of eligible patients by study for serum ferritin – ITT population**

Study	Total N	N for eligible patients
LA-01	35	8 (23%)
LA-02/06	151	65 (43%)
LA-03	24	8 (33%)
LA-04/06B	157	56 (36%)
LA08-9701	25	7 (28%)
LA-11	23	12 (52%)
LA12-9907	69	19 (28%)
LA15-002	29	18 (62%)
LA16-0102	29	5 (17%)
LA28-CMP	8	3 (38%)
LA30-0307	100	36 (36%)
Borgna-Pignatti	96	27 (28%)
<b>Total</b>	<b>746</b>	<b>264 (35%)</b>

Source: [Appendix 12.1.9.2 Statistical Appendix 3.1](#)

**Table 6.1-2 Number of eligible patients by study for liver iron concentration – ITT population**

Study	Total N	N for eligible patients
LA-01	35	15 (43%)
LA-02/06	62	0 (0%)
LA-03	25	12 (48%)
LA-04/06B	100	11 (11%)
LA08-9701	29	21 (72%)
LA-11	24	3 (13%)
LA12-9907	75	35 (47%)
LA16-0102	28	20 (71%)
LA28-CMP	2	0 (0%)
Borgna-Pignatti	2	0 (0%)
<b>Total</b>	<b>382</b>	<b>117 (31%)</b>

Source: [Appendix 12.1.9.2 Statistical Appendix 3.2](#)

**Table 6.1-3 Number of eligible patients by study for cardiac MRI T2\* – ITT population**

<b>Study</b>	<b>Total N</b>	<b>N for eligible patients</b>
LA-01	1	0 (0%)
LA-02/06	1	0 (0%)
LA-04/06B	72	10 (14%)
LA16-0102	29	29 (100%)
LA28-CMP	2	0 (0%)
<b>Total</b>	<b>105</b>	<b>39 (37%)</b>

Source: [Appendix 12.1.9.2 Statistical Appendix 3.3](#)

### 6.1.3 Demographics

The demographic characteristics of the ITT population for the primary efficacy endpoint are shown in the following table.

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**Table 7.2-1: Summary of demographic data for serum ferritin – ITT population**

	N = 264
Age (years)	
Mean ± SD	20.1 ± 12.3
(Minimum, Maximum)	(2, 76)
Sex: n (%)	
Female	145 (55)
Male	119 (45)
Ethnic Origin: n (%)	
Italian	138 (52)
Unknown	24 (9)
Egyptian	21 (8)
Iranian	18 (7)
Indonesian	12 (5)
Thai	12 (5)
Greek	11 (4)
Asian	6 (2)
Chinese	4 (2)
Asian Indian	3 (1)
Malay	2 (1)
African American	1 (0.4)
Arabic	1 (0.4)
Chinese (Jamaican)	1 (0.4)
Cypriot – Greek	1 (0.4)
East Indian	1 (0.4)
Hispanic	1 (0.4)
Indian	1 (0.4)
Italian American	1 (0.4)
Laotian	1 (0.4)
Non Hispanic	1 (0.4)
Pakistani	1 (0.4)
Spanish	1 (0.4)
Turkish	1 (0.4)
Racial Origin: n (%)	
White	194 (73)
Asian	46 (17)
Unknown	21 (8)
Black	2 (1)
Multi-racial	1 (0.4)

Source: [Appendix 12.1.9.2 Statistical Appendix 1.1](#)

**Reviewer Comments.** The population enrolled was mostly young, reflecting primarily patients with thalassemia. Only two black patients were included. The only trial in which patients from the U.S. were enrolled was LA04, the Compassionate Use Treatment Study.

The demographic characteristics of the ITT population for the secondary efficacy endpoints are shown in the following tables.

**Table 7.2-2: Summary of demographic data for LIC – ITT population**

	N = 117
Age (years)	
Mean ± SD	19.4 ± 7.0
(Minimum, Maximum)	(6, 52)
Sex: n (%)	
Female	55 (47)
Male	62 (53)
Ethnic Origin: n (%)	
Italian	68 (58)
Greek	21 (18)
Asian	5 (4)
Chinese	4 (3)
Unknown	4 (3)
Indian	3 (3)
Thai	3 (3)
Arabic	1 (1)
Asian Indian	1 (1)
Caucasian	1 (1)
East Indian	1 (1)
Greek/Italian	1 (1)
Guyanese	1 (1)
Laotian	1 (1)
Pakistani	1 (1)
Turkish	1 (1)
Racial Origin: n (%)	
White	93 (79)
Asian	21 (18)
Unknown	3 (3)

**Table 7.2-3: Summary of demographic data for cardiac MRI T2\* – ITT population**

	N = 39
Age (years)	
Mean ± SD	24.3 ± 4.7
(Minimum, Maximum)	(12, 33)
Sex: n (%)	
Female	18 (46)
Male	21 (54)
Ethnic Origin: n (%)	
Greek	16 (41)
Italian	14 (36)
Unknown	4 (10)
Asian Indian	2 (5)
Asian	1 (3)
Caucasian	1 (3)
Chinese	1 (3)
Racial Origin: n (%)	
White	31 (79)
Asian	5 (13)
Unknown	3 (8)

Source: [Appendix 12.1.9.2 Statistical Appendix 1.3](#)

**Reviewer Comments.** The demographic characteristics for the ITT populations were reasonably similar for the primary and secondary efficacy endpoints. There were more males than females in the LIC and MRI T2\* endpoint populations than in the serum ferritin populations. The relatively greater proportion of Greek enrollees for the cardiac MRI T2\* endpoint is accounted for by the fact that Study LA-16-0102 included only patients from one site in Greece and 2 sites in Italy.

#### 6.1.4 Analysis of Primary Endpoint(s)

Serum ferritin was reduced by more than 20% in 136/264 patients (52%) treated with deferiprone. Based on the fact that the lower limit of the confidence interval is 45%, the sponsor indicates that it has satisfied the hypothesis premised in the study.

There was a wide variability of success (26-100%) among the various trials as shown in the following table.

**Table 7.4.1-2 Success rate by study for serum ferritin – ITT population**

Study	Number of patients	Success rate (N, %)	95% C.I.
LA-01	8	4 (50%)	(16%, 84%)
LA-02/06	65	26 (40%)	(28%, 53%)
LA-03	8	5 (63%)	(24%, 91%)
LA-04/06B	56	29 (52%)	(38%, 65%)
LA08-9701	7	4 (57%)	(18%, 90%)
LA-11	12	10 (83%)	(52%, 98%)
LA12-9907	19	5 (26%)	(9%, 51%)
LA15-0002	18	18 (100%)	(81%, 100%)
LA16-0102	5	4 (80%)	(28%, 99%)
LA28-CMP	3	2 (67%)	(9%, 99%)
LA30-0307	36	17 (47%)	(30%, 65%)
Borgna-Pignatti	27	12 (44%)	(25%, 65%)
<b>Overall success rate</b>	<b>264</b>	<b>136 (52%)</b>	<b>(45%, 58%)</b>

Source: [Appendix 12.1.9.2 Statistical Appendix 4.2](#)

Overall, the mean serum ferritin for the ITT population fell from  $4416 \pm 2288$   $\mu\text{g/L}$  to  $3453 \pm 2099$   $\mu\text{g/L}$  within one year of therapy, a mean fall of  $962$   $\mu\text{g/L}$  ( $\pm 1907$ ).

Analysis of the PP population produced results similar to those in the ITT population.

Planned subgroup analyses were performed on six variables and all results were consistent with the results evidenced in the overall population, although persons with two or more serum ferritin determinations had higher rates of success than those with a single determination of serum ferritin, and patients outside Europe had higher rates of success than did those who were enrolled from European countries. These results are shown in the following tables.

**Table 7.4.1-6 Subgroup analysis for success rate for serum ferritin – ITT population**

<b>Subgroup</b>	<b>Number of patients</b>	<b>Success rate (N, %) (95% CI)</b>
2 or More SF <sup>a</sup>	63	45 (71%) (59%, 82%)
A Single SF	156	70 (45%) (37%, 53%)
Paediatric Patients <sup>b</sup>	83	38 (46%) (35%, 57%)
Adult Patients	181	98 (54%) (47%, 62%)
Male	119	63 (53%) (44%, 62%)
Female	145	73 (50%) (42%, 59%)
Thalassemia Major	228	115 (50%) (44%, 57%)
Non-Thalassemia Major	36	21 (58%) (41%, 74%)
European Countries	136	54 (40%) (31%, 48%)
Non-European Countries	128	82 (64%) (55%, 72%)

<sup>a</sup>Note: Among various patients for whom 2 of the 2, 2 of the 3, 3 of the 4, or 3 of the 5 serum ferritin (SF) values obtained prior to starting Ferriprox were > 2500 µg/L.

<sup>b</sup>Pediatric patients were < 16 years of age.

Adapted from Sponsor submission

**Table 7.4.1-4 Subgroup analysis for success rate for serum ferritin: GCP Studies only– ITT population**

<b>Number of patients</b>	<b>Success rate (N, %)</b>	<b>95% C.I.</b>
132	56 (42%)	(34%, 51%)

Note: GCP studies: LA-0206, LA-08, LA-12, LA-16, LA-30

Source: [Appendix 12.1.9.2 Statistical Appendix 7.6](#)

An unplanned subgroup analysis was performed for subjects who received deferiprone monotherapy, as some subjects received combination chelator therapy usually combining deferiprone with deferoxamine. The success rate in this group was 50% as shown in the following table.

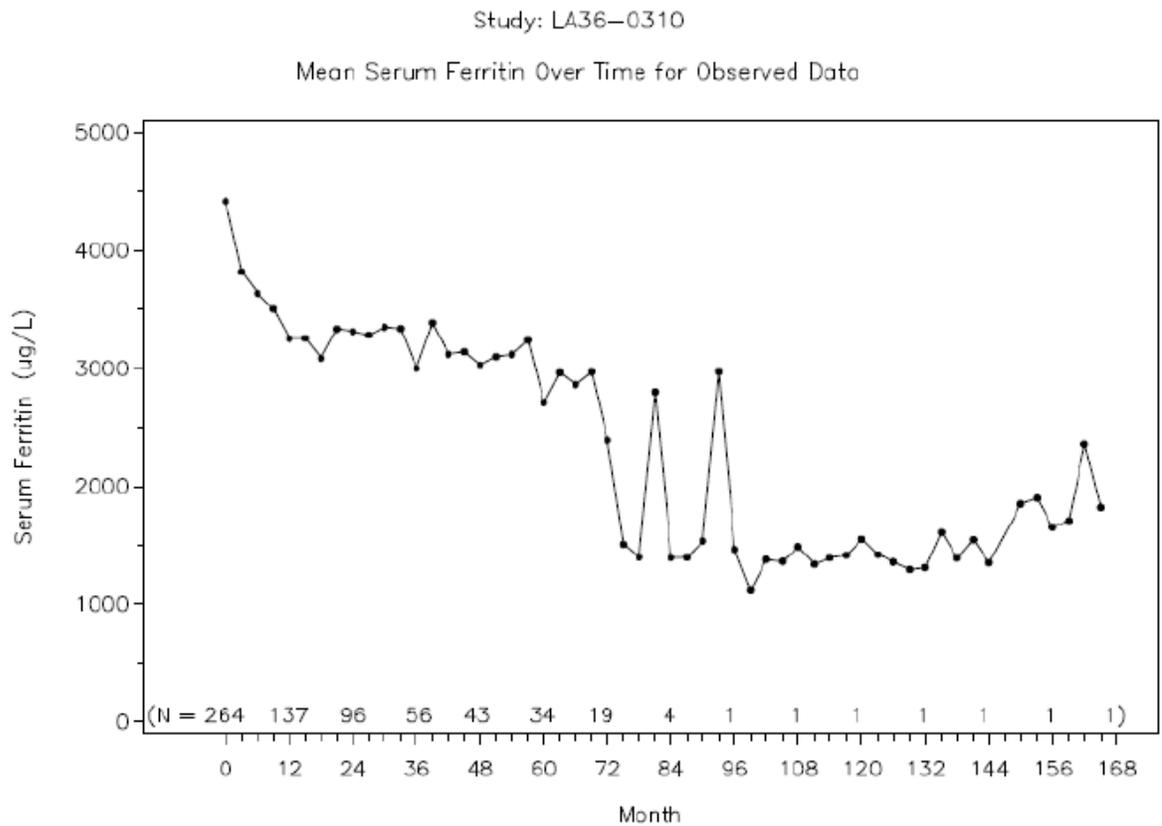
**Table 7.4.1-5 Subgroup analysis for success rate for serum ferritin: Ferriprox Monotherapy – ITT population**

<b>Number of patients</b>	<b>Success rate (N, %)</b>	<b>95% C.I.</b>
236	118 (50%)	(43%, 57%)

Source: [Appendix 12.1.9.2 Statistical Appendix 7.7](#)

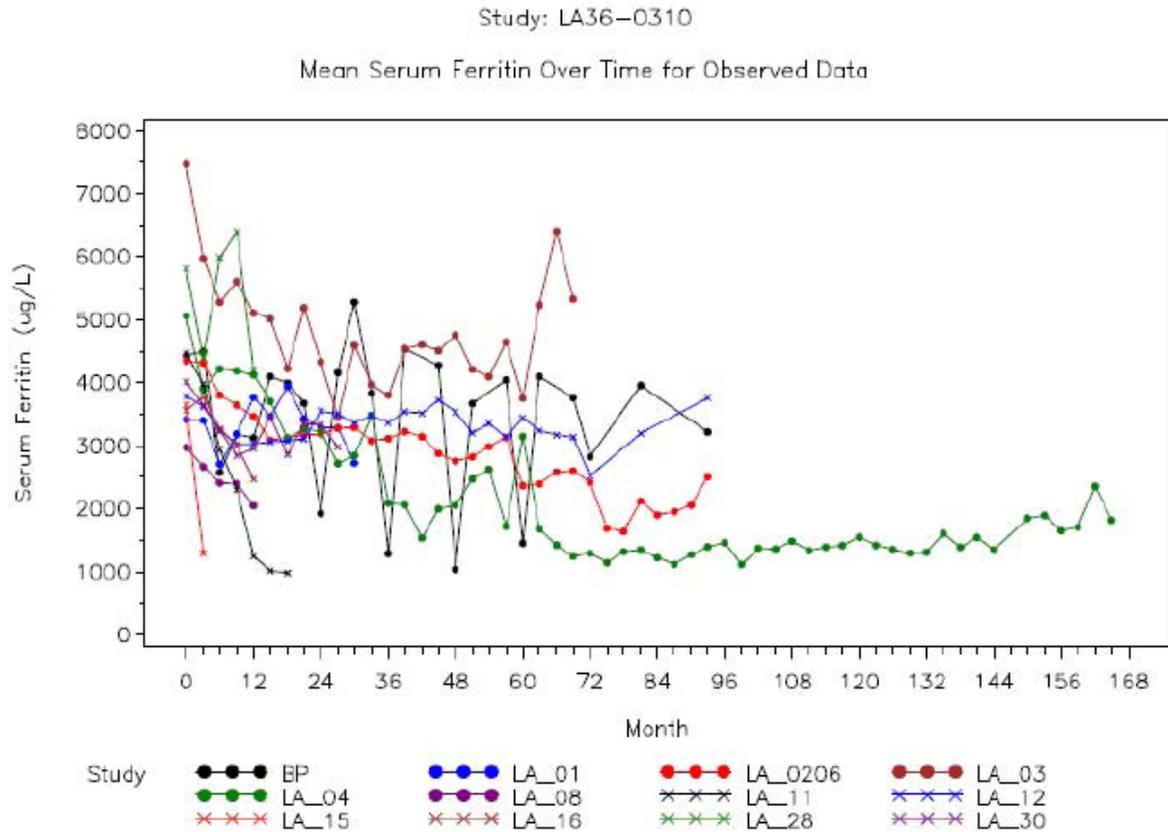
The trend for the mean serum ferritin showed a decline during the 12 months of the trial and remained approximately stable over the next 4 years as indicated in the graph below. The significance of serum ferritin values beyond a total of 5 years is uncertain because there were too few subjects who continued beyond that time.

**Figure 7.4.1-1 Mean serum ferritin values over time in patients meeting study inclusion criteria with the observed data**



The change in mean serum ferritin over the one year period of treatment with deferiprone in the different studies was quite variable as shown in the following graph.

**Figure 7.4.1-2 Mean serum ferritin over time by study in patients meeting study inclusion criteria with the observed data**



**Reviewer Comments.** In patients who failed previous chelation therapy as defined by the sponsor's criteria, deferiprone given over a period of up to one year was effective in lowering serum ferritin concentration by  $\geq 20\%$  in approximately half of the patients with transfusional hemosiderosis whose baseline serum ferritin was  $> 2500 \text{ g/L}$ .

There was significant variation in the degree of fall in mean serum ferritin among the different trials. For instance, there were early and relatively dramatic decreases in mean serum ferritin in studies LA-11 and LA-15. LA-11 was a study conducted in Thailand in which 24 patients with non-transfusion dependent thalassemia-Hemoglobin E disease experienced a fall in mean serum ferritin from  $3287 \pm 1927 \mu\text{g/dL}$  to  $1221 \pm 1667 \mu\text{g/dL}$  after one year of therapy. In that study, the mean daily dose of deferiprone was  $48 \pm 5.7 \text{ mg/kg}$  (range 15 – 78). LA-15 was a study conducted in Iran in which patients with thalassemia and hemosiderosis were treated with deferiprone for 3 months and in whom the mean serum ferritin fell

from  $3364 \pm 900 \mu\text{g/mL}$  to  $1271 \pm 302 \mu\text{g/mL}$  in that period of time. In that study, the dose of deferiprone was 75 mg/kg/d and there were no data provided on transfusion history.

The relationship between the serum ferritin and clinical outcome is not well established. There are some data that show that outcomes in patients with transfusion related hemosiderosis treated with deferoxamine who usually maintain a serum ferritin at levels below approximately 2500  $\mu\text{g/mL}$  have longer survivals compared to those patients in whom the serum ferritin remains consistently above that level (Olivieri NF et al 1994. Survival in Medically Treated Patients with Homozygous  $\beta$ -Thalassemia. NEJM; 331:574-578). In only 3 of the submitted studies (LA-11, -15 and -16) did the mean serum ferritin fall below that value after 1 year of deferiprone treatment. In Study LA-16-0102, the dose of deferiprone employed for approximately  $\frac{3}{4}$  of the treatment period was 100 mg/kg/d rather than the dose of 75 mg/kg/day that was used in most of the other studies. In the other studies, it required several years of therapy to reach a mean serum ferritin of 2500  $\mu\text{g/mL}$  or the level was never reached even after 4-5 years of therapy. Although such findings do not necessarily indicate that deferiprone is not clinically effective, they nonetheless warrant a sense of caution in interpreting the clinical utility of the drug. The data, however, may support the use of the drug in patients who have no alternative to other methods of lowering body iron burden.

The sponsor has met its benchmarks for the primary efficacy endpoint for Study LA36-0310.

### 6.1.5 Analysis of Secondary Endpoints(s)

The change in LIC after one year of treatment with deferiprone was one of the secondary endpoints for Study LA36-0310. Of 117 subjects who had a baseline and a follow-up LIC determined and who were treated with deferiprone, 49 (41%, [C.I. 32%; 51%]) had a fall in LIC of more than 20% at 1 year of observation as shown in the following table.

**Table 7.4.1-8 Overall success rate for LIC – ITT population**

Study	Number of patients	Success rate (N, %)	95% C.I.
Overall	117	49 (42%)	(33%, 51%)

Source: [Appendix 12.1.9.2 Statistical Appendix 5.1](#)

The studies from which the data were obtained and the results for each study are shown in the following table.

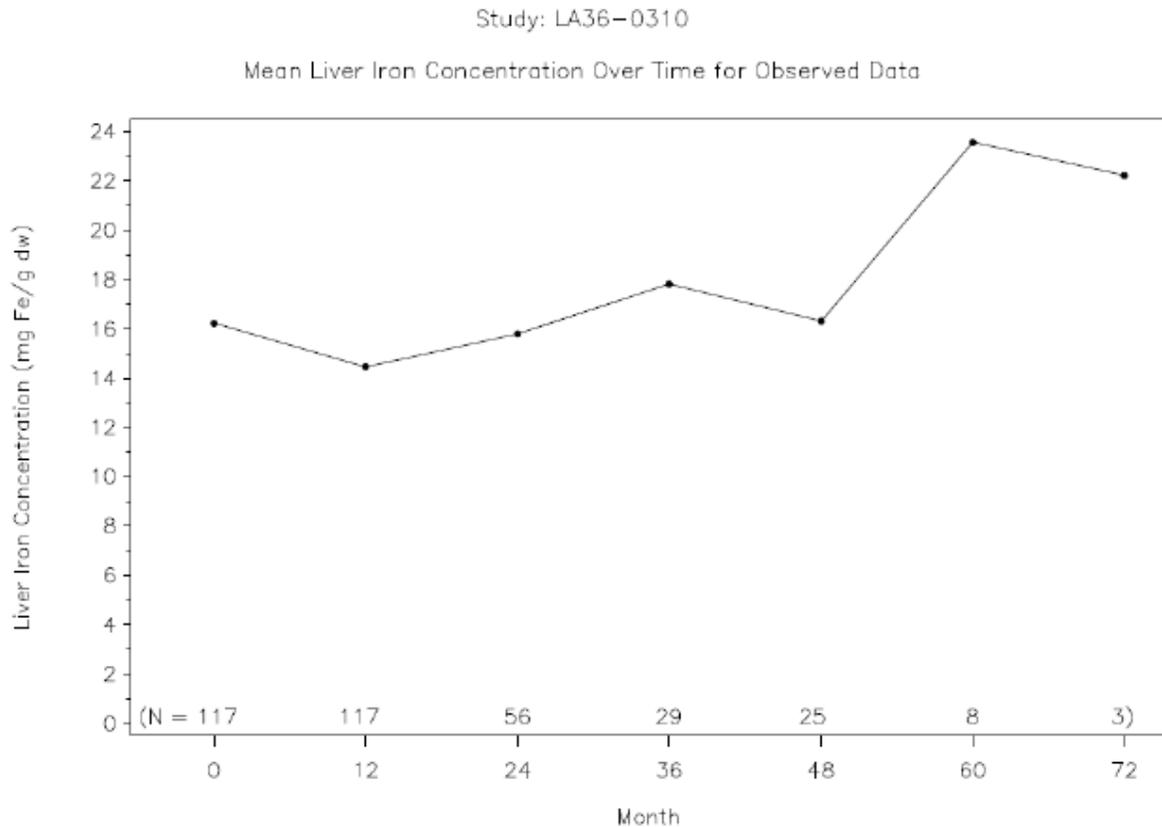
**Table 7.4.1-9 Success rate by study for LIC– ITT population**

<b>Study</b>	<b>Number of patients</b>	<b>Success rate (N, %)</b>	<b>95% C.I.</b>
LA-01	15	5 (33%)	(12%, 62%)
LA-03	12	8 (67%)	(35%, 90%)
LA-04/06B	11	4 (36%)	(11%, 69%)
LA08-9701	21	12 (57%)	(34%, 78%)
LA-11	3	2 (67%)	(9%, 99%)
LA12-9907	35	9 (26%)	(12%, 43%)
LA16-0102	20	9 (45%)	(23%, 68%)
<b>Overall success rate</b>	<b>117</b>	<b>49 (42%)</b>	<b>(33%, 51%)</b>

Source: [Appendix 12.1.9.2 Statistical Appendix 5.2](#)

The mean LIC declined from  $15.9 \pm 10.1$  to  $14.6 \pm 9.1$  mg Fe/g dw, a fall of  $1.3 \pm 6.9$  mg Fe/ g dw. However, trend analysis over time for LIC showed a decrease of 0.00189 mg Fe/g dw, and this rate of decline was not statistically significant even though 44% of subjects had a negative slope. For subjects who were treated with deferiprone for longer than 1 year, the mean LIC rose slightly at both the end of 2 years and at the end of 3 years. The number of subjects treated for 3 years or longer is quite small. These data are conveyed in the following graph.

**Figure 7.4.1-4 Mean LIC over time in patients meeting study inclusion criteria with the observed data**



**Reviewer Comments.** The sponsor has met its benchmarks for the secondary efficacy endpoint (change in LIC after 1 year of deferiprone treatment) for Study LA36-0310. However, there are some data available that indicate that the risks of hemosiderosis approach normalcy when the LIC is no greater than 7 mg Fe/ dw, and that level was achieved in only 7/117 subjects in this study. From the data presented, it appears that the treated population can be separated into responders and non-responders. It is possible that some of the non-responders experienced adverse reactions that led to drug withdrawal, were non-compliant or were given an insufficient dose of deferiprone.

The change in cardiac MRI T2\* in subjects with transfusion related hemosiderosis after treatment for 1 year was an additional secondary endpoint of Study LA36-0310. Of 39 subjects who had a baseline and a follow-up cardiac MRI T2\* determined and who were treated with deferiprone, 24 (62%, [C.I. 45%; 77%]) had an increase of more than 20% at 1 year of observation as shown in the following table.

**Table 7.4.1-12 Success rate by study for cardiac MRI T2\* – ITT population**

Study	Number of patients	Success rate (N,%)	95% C.I.
LA-04/06B	10	6 (60%)	(26%, 88%)
LA16-0102	29	18 (62%)	(42%, 79%)
<b>Overall success rate</b>	<b>39</b>	<b>24 (62%)</b>	<b>(45%, 77%)</b>

Source: [Appendix 12.1.9.2 Statistical Appendix 6.2](#)

The mean cardiac MRI T2\* rose from  $11.8 \pm 4.9$  to  $15.1 \pm 7.0$  ms, an increase of  $3.3 \pm 3.4$  ms as shown in the following table.

**Table 7.4.1-13 Descriptive statistics for cardiac MRI T2\* (ms) – ITT population**

	N	Mean $\pm$ SD (Minimum, Maximum)
Baseline	39	$11.8 \pm 4.9$ (4.0, 19.5)
Last observation within 1 year + 3 months	39	$15.1 \pm 7.0$ (3.4, 28.0)
Change	39	$3.3 \pm 3.4$ (-2.0, 12.7)

Source: [Appendix 12.1.9.2 Statistical Appendix 6.5](#)

Note: Descriptive statistics based on log-transformed MRI T2\* data were also calculated and are presented in Appendix 6.5a.

There were too few subjects who had measurements of cardiac MRI T2\* beyond 1 year of treatment to assess longer term effects on that parameter.

**Reviewer Comments.** The sponsor has met its benchmarks for the secondary efficacy endpoint (change in cardiac MRI T2\*) after 1 year of deferiprone treatment for study LA36-0310. Whether or not an increase in the measurement for cardiac MRI T2\* is a valid surrogate endpoint that predicts clinical benefit in patients with cardiac hemosiderosis is still not clear, even though it may be stated that patients with an MRI T2\* value of 10 ms or less appear to have a greater risk of developing some cardiac complication in the year following the performance of the study than patients with a value in excess of 10 ms (Kirk P at al 2009. Cardiac T2\* magnetic resonance for prediction of cardiac complications in thalassemia. Circulation; 120:1961-1968). There are no data, however, that show that increasing the value of the cardiac MRI T2\* after the administration of deferiprone is associated with a lessening of cardiac complications. As importantly, it is not known whether or not

**an increase in cardiac MRI T2\* by an average of 3.3 ms is sufficient to predict clinical improvement and whether there is some minimal rise in the value necessary to benefit a particular patient.**

#### 6.1.6 Other Endpoints

No other endpoints were analyzed.

#### 6.1.7 Subpopulations

The following subgroups/cohorts were analyzed:

1. European/non-European subjects. Non-Europeans entered the study with approximately 10% higher serum ferritin levels compared to Europeans.
2. Subset of patients from Good Clinical Practice studies/subset of patients treated with deferiprone alone.
3. Subset of patients with 2 or more serum ferritin values of  $> 2500 \mu\text{g/L}$ /subset of patients with a single serum ferritin value of  $> 2500 \mu\text{g/L}$
4. Pediatric/adult patients
5. Male/female
6. Thalassemia/non-thalassemia patients

In all subgroups analyzed, the success rate exceeded 20% in both subgroups, and the sponsor states that this indicates efficacy no matter which subgroup was analyzed.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The sponsor has not performed any significant dose-response studies. In virtually all of the trials, the dose of deferiprone employed was 75 mg/kg/d divided into 3 doses taken during each day. In study LA16-0102, subjects were commenced on that dose of deferiprone and, during the next 2 months, the dose was increased in a step-wise fashion to a total daily dose of 100 mg/kg/d for the remainder of the year of the trial. In study LA30-0307, subjects were commenced on a dose of 50 mg/kg/d and then dosed based on measurements of iron overload and the development of adverse reactions.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Most of the trials performed by the sponsor had a duration of approximately 1 year. In some of the trials, subjects were allowed to continue the drug indefinitely. There is a dearth of data available to judge the continued efficacy and/or safety of deferiprone

because there were only 34 subjects who were followed for more than 5 years while receiving deferiprone. In these patients, no new safety concerns appear to have arisen.

#### 6.1.10 Additional Efficacy Issues/Analyses

None performed or analyzed.

## 7 Review of Safety

### Safety Summary

See Pages 80 - 106, Section 7 of previous review in Appendix 9.4 for the review of safety data submitted in the original NDA. Those data (including a Day 120 Safety Report) represented data that re-integrated safety assessments through a cutoff date of February 28, 2009.

In this current submission, the sponsor has provided re-integrated safety data through a new cut-off date of August 31, 2010. In addition, safety information collected between that date and January 31, 2011 was submitted but not re-integrated.

### 7.1 Methods

The safety profile of deferiprone is based on findings from sponsor-supported clinical trials and post-marketing surveillance activities during the 11 years during which the drug has been used in the 61 countries in which it is approved. The sponsor states that it estimates that there have been more than 35,000 patient-years of exposure with the longest exposure being in excess of 14 years.

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See Pages 80 – 84, Section 7 of previous review in Appendix 9.4.

The only additional study performed by the sponsor since August 31, 2006 was study LA30-0307, which evaluated the safety and efficacy of a deferiprone oral solution (100 mg/ml) for the treatment of hemosiderosis in transfusion-dependent pediatric thalassemia patients. The study report was submitted to IND 45724 on May 29, 2009. Patients completing this study were eligible to continue receiving the oral solution through a Compassionate Use Protocol (LA28-CMP).

The sponsor has continued to provide deferiprone to patients with transfusion-related hemosiderosis in the U.S. and Canada through its long-standing compassionate use program under study LA-04.

The sponsor commenced a new study (LA35-PM) on June 6, 2010. This is a postmarketing surveillance program that seeks to evaluate the use and monitoring of deferiprone under clinical practice conditions, with assessments of both efficacy and safety.

The sponsor continues to review the published literature for reports of safety information regarding deferiprone.

### 7.1.2 Categorization of Adverse Events

See Page 85, Section 7 of previous review in Appendix 9.4

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

See Page 85, Section 7 of previous review in Appendix 9.4

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

See Pages 85 - 88, Section 7 of previous review in Appendix 9.4.

Compared to the data submitted in the original NDA, new safety data in the current submission, when re-integrated with the previous submission, result in a lower mean age, since 100/186 new subjects enrolled were children, aged 1 -10 years, who entered on to study LA30-0307, which was the evaluation of a liquid formulation of the drug. In pooled clinical studies of the re-integrated data, 642 subjects were treated with doses of deferiprone between 50 – 100 mg/kg/d. Deferiprone was co-administered with deferoxamine to an additional 89 subjects and 13 subjects were exposed to deferiprone at doses that do not match the three doses listed in the following table. The mean duration of exposure was 2.09 years (range, 0 – 14.89 years). Overall exposure after re-integration of safety data is shown in the following table.

**Table 2.1-1: Duration of Study Drug Exposure in Pooled Clinical Studies**

	FERRIPROX 50 mg/kg/d n=25 (%)	FERRIPROX 75 mg/kg/d n=407 (%)	FERRIPROX 100 mg/kg/d n=108 (%)	FERRIPROX (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with FERRIPROX n=89 (%)
Subjects Exposed [N]	25	407	108	642	118	89
Subject-Years Exposure (sum)	25.9	987.1	148.5	1338.8	129.3	134.6
Mean	1.04	2.43	1.37	2.09	1.10	1.51
SD	0.59	2.32	0.78	2.13	0.74	1.43
Median	1.23	2.15	1.02	1.34	0.99	0.98
Min, Max	0.02, 1.63	0.00, 14.89	0.08, 2.54	0.00, 14.89	0.08, 2.87	0.01, 5.60
Duration of Exposure [n(%)]						
Any Exposure	25 ( 100.0)	407 ( 100.0)	108 ( 100.0)	642 ( 100.0)	118 ( 100.0)	89 ( 100.0)
>= 1 Day	25 ( 100.0)	407 ( 100.0)	108 ( 100.0)	642 ( 100.0)	118 ( 100.0)	89 ( 100.0)
>= 1 Week	25 ( 100.0)	406 ( 99.8)	108 ( 100.0)	638 ( 99.4)	118 ( 100.0)	87 ( 97.8)
>= 1 Month	21 ( 84.0)	391 ( 96.1)	108 ( 100.0)	616 ( 96.0)	108 ( 91.5)	84 ( 94.4)
>= 6 Months	19 ( 76.0)	301 ( 74.0)	88 ( 81.5)	492 ( 76.8)	96 ( 81.4)	72 ( 80.9)
>= 1 Year	16 ( 64.0)	246 ( 60.4)	61 ( 56.5)	365 ( 56.9)	46 ( 39.0)	36 ( 40.4)
>= 2 Years	0 ( 0.0)	209 ( 51.4)	33 ( 30.6)	264 ( 41.1)	23 ( 19.5)	18 ( 20.2)
>= 3 Years	0 ( 0.0)	127 ( 31.2)	0 ( 0.0)	145 ( 22.8)	0 ( 0.0)	15 ( 16.9)
>= 4 Years	0 ( 0.0)	95 ( 23.3)	0 ( 0.0)	107 ( 16.7)	0 ( 0.0)	10 ( 11.2)
>= 5 Years	0 ( 0.0)	74 ( 18.2)	0 ( 0.0)	80 ( 12.5)	0 ( 0.0)	4 ( 4.5)
>= 6 Years	0 ( 0.0)	17 ( 4.2)	0 ( 0.0)	19 ( 3.0)	0 ( 0.0)	0 ( 0.0)
>= 7 Years	0 ( 0.0)	7 ( 1.7)	0 ( 0.0)	9 ( 1.4)	0 ( 0.0)	0 ( 0.0)
>= 8 Years	0 ( 0.0)	6 ( 1.5)	0 ( 0.0)	8 ( 1.2)	0 ( 0.0)	0 ( 0.0)
>= 9 Years	0 ( 0.0)	6 ( 1.5)	0 ( 0.0)	8 ( 1.2)	0 ( 0.0)	0 ( 0.0)
>= 10 Years	0 ( 0.0)	4 ( 1.0)	0 ( 0.0)	6 ( 0.9)	0 ( 0.0)	0 ( 0.0)
>= 11 Years	0 ( 0.0)	3 ( 0.7)	0 ( 0.0)	5 ( 0.8)	0 ( 0.0)	0 ( 0.0)
>= 12 Years	0 ( 0.0)	3 ( 0.7)	0 ( 0.0)	5 ( 0.8)	0 ( 0.0)	0 ( 0.0)
>= 13 Years	0 ( 0.0)	3 ( 0.7)	0 ( 0.0)	5 ( 0.8)	0 ( 0.0)	0 ( 0.0)
>= 14 Years	0 ( 0.0)	3 ( 0.7)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)

- 1) Percentage is calculated based on the number of subjects exposed with systemic iron overload primary diagnoses in each dosing group.
- 2) Subjects exposed to more than one Ferriprox dose are classified by their maximum dose.
- 3) There are 13 subjects, whose maximum dose of Ferriprox is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These subjects are included in Ferriprox (all doses) and were exposed for a total of 42.6 subject-years.
- 4) Duration of Exposure (days) is calculated as ((End Date of Exposure - Start Date of Exposure +1) - sum of interruption days), 1 month is taken to be equivalent to 30.5 days.
- 5) Data cutoff date: 31Aug2010

Based on sales data, the sponsor estimates that there have been 33,725 patient-years of exposure to deferiprone tablets and 318 patient-years of exposure to deferiprone oral solution.

**Reviewer Comments. The sponsor has not adequately studied multiple doses of deferiprone to determine the optimal dose usage for varying body iron burdens. The majority of patients (407/642, 63.4%) were treated with a daily dose of 75 mg/kg/d and it is primarily in that group that the duration of therapy has exceeded**

**1 year. Only 88 patients were treated at a dose of 100 mg/kg/d for a duration of more than 6 months, 61 were treated for more than 1 year, 33 were treated for more than 2 years and none was treated with that dose for more than 3 years. Therefore, evidence for the efficacy and safety of doses of deferiprone greater than 75 mg/kg/d for the required time of treatment for likely recipients of the drug is quite limited.**

The demographic characteristics of the patients treated with deferiprone in clinical trials are shown in the next table.

**Table 3.1-1: Combined Demographic Profile in Pooled Clinical Studies**

	Ferriprox 50 mg/kg/d n=25 (%)	Ferriprox 75 mg/kg/d n=407 (%)	Ferriprox 100 mg/kg/d n=108 (%)	Ferriprox (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with Ferriprox n=89 (%)
<b>Age (Years)</b>						
N	25	407	108	642	118	89
Mean	33.2	20.7	14.7	20.7	20.4	24.3
SD	12.1	13.2	12.7	13.3	6.8	9.5
Median	32.0	18.0	8.5	19.0	20.0	23.0
Min, Max	5, 62	1, 77	1, 70	1, 77	6, 35	10, 54
<b>Age [n(%)]</b>						
1 - 5 Years	1 ( 4.0)	25 ( 6.1)	33 ( 30.6)	61 ( 9.5)	0 ( 0.0)	0 ( 0.0)
6 - 11 Years	0 ( 0.0)	40 ( 9.8)	31 ( 28.7)	81 ( 12.6)	15 ( 12.7)	6 ( 6.7)
12 - 15 Years	0 ( 0.0)	72 ( 17.7)	0 ( 0.0)	80 ( 12.5)	16 ( 13.6)	7 ( 7.9)
16 - 17 Years	2 ( 8.0)	44 ( 10.8)	0 ( 0.0)	51 ( 7.9)	10 ( 8.5)	4 ( 4.5)
>= 18 Years	22 ( 88.0)	228 ( 55.5)	44 ( 40.7)	369 ( 57.5)	77 ( 65.3)	72 ( 80.9)
<b>Sex [n(%)]</b>						
Male	17 ( 68.0)	197 ( 48.4)	57 ( 52.8)	320 ( 49.8)	56 ( 47.5)	44 ( 49.4)
Female	8 ( 32.0)	210 ( 51.8)	51 ( 47.2)	322 ( 50.2)	62 ( 52.5)	45 ( 50.8)
<b>Race [n(%)]</b>						
White	1 ( 4.0)	333 ( 81.8)	71 ( 65.7)	467 ( 71.2)	103 ( 87.3)	50 ( 56.2)
Black	0 ( 0.0)	3 ( 0.7)	0 ( 0.0)	4 ( 0.6)	1 ( 0.8)	1 ( 1.1)
Asian	24 ( 96.0)	34 ( 8.4)	33 ( 30.6)	114 ( 17.8)	14 ( 11.9)	14 ( 15.7)
Unknown	0 ( 0.0)	36 ( 8.8)	2 ( 1.9)	59 ( 9.2)	0 ( 0.0)	20 ( 22.5)
Multi-Racial	0 ( 0.0)	1 ( 0.2)	2 ( 1.9)	8 ( 1.2)	0 ( 0.0)	4 ( 4.5)

- 1) Percentage is calculated based on the number of subjects exposed with systemic iron overload primary diagnoses in each dosing group.
- 2) Subjects exposed to more than one Ferriprox dose are classified by their maximum dose.
- 3) There are 13 subjects, whose maximum dose of Ferriprox is other than 50, 75 or 100, not exceeding 100 mg/kg/day.
- 4) The Age when subjects were first exposed to Ferriprox is used.
- 5) Out of 642 subjects 222 were pediatric (< 16 years old) and 420 were adults (>=16 years old).
- 6) Data cutoff date: 31Aug2010

**Reviewer Comments. The mean age of the subjects exposed was 20.7 years reflecting the fact that the majority of subjects who were enrolled had a base diagnosis of thalassemia. There was a representation of pediatric patients but most of these were patients treated with the liquid oral formulation of the drug at a dose of 100 mg/kg/d. Most of the subjects were white with most of the remaining being Asians. Only 4 black subjects were included in the clinical trials.**

The baseline characteristics of the patients treated with deferiprone are shown in the following table.

**Table 3.2-1: Baseline Characteristics of Subjects in Pooled Clinical Studies**

	Ferriprox 50 mg/kg/d n=25 (%)	Ferriprox 75 mg/kg/d n=407 (%)	Ferriprox 100 mg/kg/d n=108 (%)	Ferriprox (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with Ferriprox n=89 (%)
<b>Primary Disease (Sponsor Defined) [n (%)]</b>						
Aplasia Pure Red Cell	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
Aplastic Anemia	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
Blackfan-Diamond Anemia	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
Chronic Lymphocytic Leukemia	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
Congenital Anaemia	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	2 ( 2.2)
Hemoglobin E-Thalassemia Disease	24 ( 96.0)	1 ( 0.2)	9 ( 8.3)	42 ( 6.5)	0 ( 0.0)	5 ( 5.6)
Hereditary Haemochromatosis	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
Myelodysplasia	0 ( 0.0)	12 ( 2.9)	1 ( 0.9)	15 ( 2.3)	0 ( 0.0)	1 ( 1.1)
Myelofibrosis	0 ( 0.0)	4 ( 1.0)	0 ( 0.0)	4 ( 0.6)	0 ( 0.0)	0 ( 0.0)
Refractory Anaemia	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
Severe Hemolytic Anemia	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
Sickle Cell Disease	0 ( 0.0)	4 ( 1.0)	1 ( 0.9)	5 ( 0.8)	0 ( 0.0)	0 ( 0.0)
Thalassemia Intermedia	0 ( 0.0)	4 ( 1.0)	0 ( 0.0)	5 ( 0.8)	0 ( 0.0)	1 ( 1.1)
Thalassemia Major	1 ( 4.0)	375 ( 92.1)	97 ( 89.8)	580 ( 87.2)	118 ( 100.0)	78 ( 87.8)
Transfusion Dependent Aase Syndrome	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
Transfusion Dependent Refractory Anemia	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
<b>Baseline Splenectomy Status [n(%)]</b>						
Positive	0 ( 0.0)	135 ( 33.2)	18 ( 16.7)	204 ( 31.8)	18 ( 15.3)	49 ( 55.1)
Negative	1 ( 4.0)	204 ( 50.1)	90 ( 83.3)	345 ( 53.7)	54 ( 45.8)	40 ( 44.9)
Missing Data	24 ( 96.0)	68 ( 16.7)	0 ( 0.0)	93 ( 14.5)	46 ( 39.0)	0 ( 0.0)

	Ferriprox 50 mg/kg/d n=25 (%)	Ferriprox 75 mg/kg/d n=407 (%)	Ferriprox 100 mg/kg/d n=108 (%)	Ferriprox (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with Ferriprox n=89 (%)
<b>Baseline Hepatitis C Status [n(%)]</b>						
Positive	0 ( 0.0)	208 ( 51.1)	30 ( 27.8)	258 ( 40.2)	52 ( 44.1)	17 ( 19.1)
Negative	1 ( 4.0)	175 ( 43.0)	64 ( 59.3)	279 ( 43.5)	66 ( 55.9)	36 ( 40.4)
Missing Data	24 ( 96.0)	24 ( 5.9)	14 ( 13.0)	105 ( 16.4)	0 ( 0.0)	36 ( 40.4)
<b>Baseline Serum Ferritin [n(%)]</b>						
<= 2,500 µg/L	10 ( 40.0)	229 ( 56.3)	60 ( 55.6)	356 ( 55.5)	79 ( 66.9)	49 ( 55.1)
> 2,500 µg/L	14 ( 56.0)	177 ( 43.5)	48 ( 44.4)	284 ( 44.2)	39 ( 33.1)	40 ( 44.9)
Missing Data	1 ( 4.0)	1 ( 0.2)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	0 ( 0.0)
<b>Baseline ALT [n(%)]</b>						
<= 2 x ULN	21 ( 84.0)	316 ( 77.6)	95 ( 88.0)	511 ( 79.6)	97 ( 82.2)	70 ( 78.7)
> 2 x ULN	4 ( 16.0)	90 ( 22.1)	13 ( 12.0)	130 ( 20.2)	21 ( 17.8)	19 ( 21.3)
Missing Data	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
<b>Baseline ANC [n(%)]</b>						
< 1.5 x 10/L	0 ( 0.0)	6 ( 1.5)	0 ( 0.0)	8 ( 1.2)	1 ( 0.8)	2 ( 2.2)
>=1.5 x 10/L	25 ( 100.0)	400 ( 98.3)	108 ( 100.0)	633 ( 98.6)	117 ( 99.2)	87 ( 97.8)
Missing Data	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)

1) Percentage is calculated based on the number of subjects exposed with systemic iron overload primary diagnoses in each dosing group.

2) Subjects exposed to more than one Ferriprox dose are classified by their maximum dose.

3) There are 13 subjects whose maximum dose of Ferriprox is other than 50, 75 or 100, not exceeding 100 mg/kg/day.

4) Data cutoff date: 31Aug2010

**Reviewer Comments. Thalassemia (beta or E-thalassemia) was the cause for anemia in 93.7% of patients. There was minimal representation of patients with myelodysplastic syndrome (15 patients, 2.3% of all enrollees). Patients with sickle cell disease numbered only 5 (0.8%). The baseline serum ferritin was > 2500 µg/L in 44.2% of enrolled subjects.**

## 7.2.2 Explorations for Dose Response

See Page 89, Section 7.2.2 of previous review in Appendix 9.4

The current submission adds 100 subjects who received deferiprone at a dose of up to 100 mg/kg/d to the previous submission. About ½ of these subjects were between the ages of 1 -11 years. There was no remarkable difference in the frequency or type of adverse reactions based on dose, although an increase in dose appeared to be associated with a decrease in gastrointestinal complaints, and an increase in the frequency of “neutrophils decreased” (0% at 50 mg/kg/d, 6.9% at a dose of 75 mg/kg/d and 19.4% at a dose of 100 mg/kg/d), the development of neutropenia (4.0% at a dose of 50 mg/kg/d, 7.1% at a dose of 75 mg/kg/d and 7.4% at a dose of 100 mg/kg/d), elevation of alanine aminotransferase and in body weight. Adverse reactions occurred less frequently in

children between the ages of 1 – 5 years compared to all other age groups. These data are shown in the following 2 tables.

**Table 4.1-1: Summary of On-Treatment Adverse Events in Pooled Clinical Studies Occurring in >5% Subjects**

Body System Preferred Term	FERRIPROX 50 mg/kg/d n=25 (%)	FERRIPROX 75 mg/kg/d n=407 (%)	FERRIPROX 100 mg/kg/d n=108 (%)	FERRIPROX (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with FERRIPROX n=89 (%)
SUBJECTS WITH ANY AE	23 ( 92.0)	346 ( 85.0)	94 ( 87.0)	538 ( 83.8)	100 ( 84.7)	68 ( 76.4)
SUBJECTS WITH ANY AE OCCURRING IN > 5%	19 ( 76.0)	329 ( 80.8)	81 ( 75.0)	486 ( 75.7)	93 ( 78.8)	52 ( 58.4)
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>						
NEUTROPENIA	1 ( 4.0)	40 ( 9.8)	8 ( 7.4)	56 ( 8.7)	10 ( 8.5)	5 ( 5.6)
LYMPHADENOPATHY	1 ( 4.0)	29 ( 7.1)	8 ( 7.4)	43 ( 6.7)	5 ( 4.2)	5 ( 5.6)
	0 ( 0.0)	11 ( 2.7)	0 ( 0.0)	13 ( 2.0)	6 ( 5.1)	0 ( 0.0)
<b>GASTROINTESTINAL DISORDERS</b>						
NAUSEA	15 ( 60.0)	197 ( 48.4)	37 ( 34.3)	272 ( 42.4)	36 ( 30.5)	21 ( 23.6)
VOMITING	9 ( 36.0)	87 ( 21.4)	13 ( 12.0)	117 ( 18.2)	3 ( 2.5)	7 ( 7.9)
ABDOMINAL PAIN UPPER	2 ( 8.0)	76 ( 18.7)	17 ( 15.7)	109 ( 16.8)	14 ( 11.9)	12 ( 13.5)
ABDOMINAL PAIN	0 ( 0.0)	64 ( 15.7)	11 ( 10.2)	79 ( 12.3)	10 ( 8.5)	2 ( 2.2)
DIARRHOEA	0 ( 0.0)	63 ( 15.5)	10 ( 9.3)	76 ( 11.8)	11 ( 9.3)	2 ( 2.2)
TOOTHACHE	7 ( 28.0)	46 ( 11.3)	10 ( 9.3)	73 ( 11.4)	5 ( 4.2)	10 ( 11.2)
	0 ( 0.0)	47 ( 11.5)	3 ( 2.8)	53 ( 8.3)	9 ( 7.6)	3 ( 3.4)
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>						
PYREXIA	3 ( 12.0)	169 ( 41.5)	19 ( 17.6)	210 ( 32.7)	37 ( 31.4)	16 ( 18.0)
FATIGUE	3 ( 12.0)	147 ( 36.1)	14 ( 13.0)	181 ( 28.2)	15 ( 12.7)	15 ( 16.9)
ASTHENIA	0 ( 0.0)	28 ( 6.4)	2 ( 1.9)	31 ( 4.8)	10 ( 8.5)	2 ( 2.2)
MALaise	0 ( 0.0)	18 ( 4.4)	3 ( 2.8)	21 ( 3.3)	9 ( 7.6)	0 ( 0.0)
INJECTION SITE PAIN	0 ( 0.0)	7 ( 1.7)	0 ( 0.0)	8 ( 1.2)	10 ( 8.5)	0 ( 0.0)
	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	12 ( 10.2)	0 ( 0.0)
<b>INFECTIONS AND INFESTATIONS</b>						
	9 ( 36.0)	232 ( 57.0)	47 ( 43.5)	317 ( 49.4)	71 ( 60.2)	28 ( 31.5)

NASOPHARYNGITIS	1 ( 4.0)	154 ( 37.8)	15 ( 13.9)	182 ( 28.3)	44 ( 37.3)	11 ( 12.4)
PHARYNGITIS	0 ( 0.0)	113 ( 27.8)	26 ( 24.1)	149 ( 23.2)	23 ( 19.5)	10 ( 11.2)
INFLUENZA	0 ( 0.0)	120 ( 29.5)	1 ( 0.9)	127 ( 19.8)	15 ( 12.7)	6 ( 6.7)
TONSILLITIS	1 ( 4.0)	35 ( 8.6)	1 ( 0.9)	40 ( 6.2)	2 ( 1.7)	3 ( 3.4)
BRONCHITIS	1 ( 4.0)	31 ( 7.6)	2 ( 1.9)	38 ( 5.8)	3 ( 2.5)	1 ( 1.1)
UPPER RESPIRATORY TRACT INFECTION	8 ( 32.0)	14 ( 3.4)	6 ( 5.6)	35 ( 5.5)	7 ( 5.9)	6 ( 6.7)
EAR INFECTION	0 ( 0.0)	31 ( 7.6)	0 ( 0.0)	33 ( 5.1)	1 ( 0.8)	1 ( 1.1)
RHINITIS	0 ( 0.0)	17 ( 4.2)	11 ( 10.2)	30 ( 4.7)	6 ( 5.1)	2 ( 2.2)
PHARYNGOTONSILLITIS	0 ( 0.0)	20 ( 4.9)	0 ( 0.0)	23 ( 3.6)	6 ( 5.1)	3 ( 3.4)
VIRAL INFECTION	0 ( 0.0)	10 ( 2.5)	7 ( 6.5)	19 ( 3.0)	10 ( 8.5)	1 ( 1.1)
GASTROENTERITIS	0 ( 0.0)	12 ( 2.9)	3 ( 2.8)	17 ( 2.6)	7 ( 5.9)	2 ( 2.2)
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>	<b>0 ( 0.0)</b>	<b>13 ( 3.2)</b>	<b>4 ( 3.7)</b>	<b>19 ( 3.0)</b>	<b>12 ( 10.2)</b>	<b>2 ( 2.2)</b>
TRANSFUSION REACTION	0 ( 0.0)	10 ( 2.5)	4 ( 3.7)	15 ( 2.3)	6 ( 5.1)	1 ( 1.1)
CONTUSION	0 ( 0.0)	3 ( 0.7)	0 ( 0.0)	4 ( 0.6)	6 ( 5.1)	1 ( 1.1)
<b>INVESTIGATIONS</b>	<b>2 ( 8.0)</b>	<b>110 ( 27.0)</b>	<b>46 ( 42.6)</b>	<b>174 ( 27.1)</b>	<b>17 ( 14.4)</b>	<b>13 ( 14.6)</b>
BIOPSY LIVER	0 ( 0.0)	66 ( 16.2)	0 ( 0.0)	70 ( 10.9)	1 ( 0.8)	2 ( 2.2)
NEUTROPHIL COUNT DECREASED	0 ( 0.0)	28 ( 6.9)	21 ( 19.4)	57 ( 8.9)	4 ( 3.4)	7 ( 7.9)
ALANINE AMINOTRANSFERASE INCREASED	0 ( 0.0)	29 ( 7.1)	22 ( 20.4)	58 ( 8.7)	5 ( 4.2)	4 ( 4.5)
WEIGHT INCREASED	0 ( 0.0)	3 ( 0.7)	12 ( 11.1)	17 ( 2.6)	6 ( 5.1)	1 ( 1.1)
WHITE BLOOD CELL COUNT DECREASED	0 ( 0.0)	1 ( 0.2)	5 ( 4.6)	6 ( 0.9)	6 ( 5.1)	0 ( 0.0)
WEIGHT DECREASED	2 ( 8.0)	0 ( 0.0)	1 ( 0.9)	3 ( 0.5)	9 ( 7.6)	0 ( 0.0)

Body System Preferred Term	FERRIPROX 50 mg/kg/d n=25 (%)	FERRIPROX 75 mg/kg/d n=407 (%)	FERRIPROX 100 mg/kg/d n=108 (%)	FERRIPROX (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with FERRIPROX n=89 (%)
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>	<b>5 ( 20.0)</b>	<b>115 ( 28.3)</b>	<b>21 ( 19.4)</b>	<b>157 ( 24.5)</b>	<b>36 ( 30.5)</b>	<b>14 ( 15.7)</b>
ARTHRALGIA	2 ( 8.0)	76 ( 18.7)	14 ( 13.0)	101 ( 15.7)	9 ( 7.6)	7 ( 7.9)
BACK PAIN	3 ( 12.0)	66 ( 16.2)	12 ( 11.1)	90 ( 14.0)	29 ( 24.6)	9 ( 10.1)
PAIN IN EXTREMITY	0 ( 0.0)	23 ( 5.7)	2 ( 1.9)	29 ( 4.5)	8 ( 6.8)	3 ( 3.4)
<b>NERVOUS SYSTEM DISORDERS</b>	<b>0 ( 0.0)</b>	<b>129 ( 31.7)</b>	<b>17 ( 15.7)</b>	<b>156 ( 24.3)</b>	<b>38 ( 32.2)</b>	<b>9 ( 10.1)</b>
HEADACHE	0 ( 0.0)	129 ( 31.7)	17 ( 15.7)	156 ( 24.3)	38 ( 32.2)	9 ( 10.1)
<b>RENAL AND URINARY DISORDERS</b>	<b>0 ( 0.0)</b>	<b>94 ( 23.1)</b>	<b>0 ( 0.0)</b>	<b>94 ( 14.6)</b>	<b>0 ( 0.0)</b>	<b>0 ( 0.0)</b>
CHROMATURIA	0 ( 0.0)	94 ( 23.1)	0 ( 0.0)	94 ( 14.6)	0 ( 0.0)	0 ( 0.0)
<b>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</b>	<b>0 ( 0.0)</b>	<b>12 ( 2.9)</b>	<b>3 ( 2.8)</b>	<b>15 ( 2.3)</b>	<b>7 ( 5.9)</b>	<b>0 ( 0.0)</b>
DYSMENORRHOEA	0 ( 0.0)	12 ( 2.9)	3 ( 2.8)	15 ( 2.3)	7 ( 5.9)	0 ( 0.0)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>	<b>2 ( 8.0)</b>	<b>148 ( 36.4)</b>	<b>5 ( 4.6)</b>	<b>164 ( 25.5)</b>	<b>34 ( 28.8)</b>	<b>7 ( 7.9)</b>
COUGH	0 ( 0.0)	117 ( 28.7)	4 ( 3.7)	129 ( 20.1)	25 ( 21.2)	6 ( 6.7)
OROPHARYNGEAL PAIN	2 ( 8.0)	83 ( 20.4)	1 ( 0.9)	89 ( 13.9)	18 ( 15.3)	2 ( 2.2)

- 1) On-Treatment Adverse Events are coded with MedDRA Dictionary Version 13.0
- 2) Percentage is calculated based on the number of subjects exposed with systemic iron overload primary diagnoses in each dosing group. The table is filtered for any MedDRA PT with >5% in the Ferriprox all doses or DFO columns. %Body System is calculated by the number of unique patients with PTs that appear on the report.
- 3) Subjects exposed to more than one Ferriprox dose are classified by their maximum dose.
- 4) There are 13 subjects whose maximum dose of Ferriprox is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These Subjects are included in Ferriprox (all doses)
- 5) Data cutoff date: 31 Aug 2010

**Table 4.1-2: Summary of On-Treatment Adverse Events in Pooled Clinical Studies Occurring in >5% Subjects, Stratified by Age**

Body System Preferred Term	FERRIPROX (all doses)				DFO			
	1-5 years n=61 (%)	6-11 years n=81 (%)	12-15 years n=80 (%)	>=16 years n=420 (%)	1-5 years n= 0 (%)	6-11 years n=15 (%)	12-15 years n=16 (%)	>=16 years n=87 (%)
<b>SUBJECTS WITH ANY AE OCCURRING IN &gt; 5%</b>	<b>35 ( 57.4)</b>	<b>65 ( 80.2)</b>	<b>66 ( 82.5)</b>	<b>320 ( 76.2)</b>	<b>0 ( 0.0)</b>	<b>11 ( 73.3)</b>	<b>13 ( 81.3)</b>	<b>69 ( 79.3)</b>
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>	<b>7 ( 11.5)</b>	<b>4 ( 4.9)</b>	<b>12 ( 15.0)</b>	<b>33 ( 7.9)</b>	<b>0 ( 0.0)</b>	<b>1 ( 6.7)</b>	<b>3 ( 18.8)</b>	<b>6 ( 6.9)</b>
LYMPHADENOPATHY	0 ( 0.0)	1 ( 1.2)	4 ( 5.0)	8 ( 1.9)	0 ( 0.0)	1 ( 6.7)	1 ( 6.3)	4 ( 4.6)
NEUTROPENIA	7 ( 11.5)	3 ( 3.7)	8 ( 10.0)	25 ( 6.0)	0 ( 0.0)	0 ( 0.0)	3 ( 18.8)	2 ( 2.3)
<b>GASTROINTESTINAL DISORDERS</b>	<b>7 ( 11.5)</b>	<b>30 ( 37.0)</b>	<b>39 ( 48.8)</b>	<b>196 ( 46.7)</b>	<b>0 ( 0.0)</b>	<b>4 ( 26.7)</b>	<b>7 ( 43.8)</b>	<b>25 ( 28.7)</b>
ABDOMINAL PAIN	2 ( 3.3)	15 ( 18.5)	14 ( 17.5)	45 ( 10.7)	0 ( 0.0)	1 ( 6.7)	2 ( 12.5)	8 ( 9.2)
ABDOMINAL PAIN UPPER	1 ( 1.6)	6 ( 7.4)	14 ( 17.5)	58 ( 13.8)	0 ( 0.0)	2 ( 13.3)	1 ( 6.3)	7 ( 8.0)
DIARRHOEA	1 ( 1.6)	2 ( 2.5)	9 ( 11.3)	61 ( 14.5)	0 ( 0.0)	1 ( 6.7)	1 ( 6.3)	3 ( 3.4)
NAUSEA	0 ( 0.0)	2 ( 2.5)	13 ( 16.3)	102 ( 24.3)	0 ( 0.0)	0 ( 0.0)	1 ( 6.3)	2 ( 2.3)
TOOTHACHE	0 ( 0.0)	4 ( 4.9)	3 ( 3.8)	46 ( 11.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	9 ( 10.3)
VOMITING	4 ( 6.6)	14 ( 17.3)	16 ( 20.0)	74 ( 17.6)	0 ( 0.0)	1 ( 6.7)	5 ( 31.3)	8 ( 9.2)
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>	<b>7 ( 11.5)</b>	<b>19 ( 23.5)</b>	<b>36 ( 45.0)</b>	<b>148 ( 35.2)</b>	<b>0 ( 0.0)</b>	<b>7 ( 46.7)</b>	<b>6 ( 37.5)</b>	<b>24 ( 27.6)</b>
ASTHENIA	0 ( 0.0)	0 ( 0.0)	1 ( 1.3)	20 ( 4.8)	0 ( 0.0)	1 ( 6.7)	1 ( 6.3)	7 ( 8.0)
FATIGUE	0 ( 0.0)	2 ( 2.5)	3 ( 3.8)	26 ( 6.2)	0 ( 0.0)	2 ( 13.3)	1 ( 6.3)	7 ( 8.0)
INJECTION SITE PAIN	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	3 ( 20.0)	3 ( 18.8)	6 ( 6.9)
MALAISE	0 ( 0.0)	1 ( 1.2)	3 ( 3.8)	4 ( 1.0)	0 ( 0.0)	4 ( 26.7)	3 ( 18.8)	3 ( 3.4)
PYREXIA	7 ( 11.5)	19 ( 23.5)	34 ( 42.5)	121 ( 28.8)	0 ( 0.0)	3 ( 20.0)	3 ( 18.8)	9 ( 10.3)
<b>INFECTIONS AND INFESTATIONS</b>	<b>11 ( 18.0)</b>	<b>42 ( 51.9)</b>	<b>55 ( 68.8)</b>	<b>209 ( 49.8)</b>	<b>0 ( 0.0)</b>	<b>7 ( 46.7)</b>	<b>10 ( 62.5)</b>	<b>54 ( 62.1)</b>
BRONCHITIS	0 ( 0.0)	2 ( 2.5)	4 ( 5.0)	30 ( 7.1)	0 ( 0.0)	0 ( 0.0)	1 ( 6.3)	2 ( 2.3)
EAR INFECTION	0 ( 0.0)	6 ( 7.4)	9 ( 11.3)	18 ( 4.3)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 1.1)
GASTROENTERITIS	0 ( 0.0)	2 ( 2.5)	3 ( 3.8)	12 ( 2.9)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	7 ( 8.0)
INFLUENZA	0 ( 0.0)	15 ( 18.5)	35 ( 43.8)	77 ( 18.3)	0 ( 0.0)	3 ( 20.0)	2 ( 12.5)	10 ( 11.5)
NASOPHARYNGITIS	6 ( 9.8)	24 ( 29.6)	39 ( 48.8)	113 ( 26.9)	0 ( 0.0)	5 ( 33.3)	8 ( 50.0)	31 ( 35.6)
PHARYNGITIS	8 ( 13.1)	25 ( 30.9)	29 ( 36.3)	87 ( 20.7)	0 ( 0.0)	0 ( 0.0)	2 ( 12.5)	21 ( 24.1)
PHARYNGOTONSILLITIS	0 ( 0.0)	3 ( 3.7)	8 ( 10.0)	12 ( 2.9)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	6 ( 6.9)
RHINITIS	1 ( 1.6)	5 ( 6.2)	0 ( 0.0)	24 ( 5.7)	0 ( 0.0)	0 ( 0.0)	1 ( 6.3)	5 ( 5.7)
TONSILLITIS	0 ( 0.0)	5 ( 6.2)	8 ( 10.0)	27 ( 6.4)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 2.3)
UPPER RESPIRATORY TRACT INFECTION	2 ( 3.3)	3 ( 3.7)	5 ( 6.3)	25 ( 6.0)	0 ( 0.0)	0 ( 0.0)	1 ( 6.3)	6 ( 6.9)
VIRAL INFECTION	0 ( 0.0)	0 ( 0.0)	3 ( 3.8)	16 ( 3.8)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	10 ( 11.5)
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>	<b>0 ( 0.0)</b>	<b>1 ( 1.2)</b>	<b>3 ( 3.8)</b>	<b>15 ( 3.6)</b>	<b>0 ( 0.0)</b>	<b>1 ( 6.7)</b>	<b>1 ( 6.3)</b>	<b>10 ( 11.5)</b>
CONTUSION	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	4 ( 1.0)	0 ( 0.0)	1 ( 6.7)	0 ( 0.0)	5 ( 5.7)
TRANSFUSION REACTION	0 ( 0.0)	1 ( 1.2)	3 ( 3.8)	11 ( 2.6)	0 ( 0.0)	0 ( 0.0)	1 ( 6.3)	5 ( 5.7)
<b>INVESTIGATIONS</b>	<b>24 ( 39.3)</b>	<b>21 ( 25.9)</b>	<b>23 ( 28.8)</b>	<b>106 ( 25.2)</b>	<b>0 ( 0.0)</b>	<b>0 ( 0.0)</b>	<b>1 ( 6.3)</b>	<b>16 ( 18.4)</b>
ALANINE AMINOTRANSFERASE INCREASED	10 ( 16.4)	5 ( 6.2)	8 ( 10.0)	33 ( 7.9)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	5 ( 5.7)
BIOPSY LIVER	0 ( 0.0)	3 ( 3.7)	19 ( 23.8)	48 ( 11.4)	0 ( 0.0)	0 ( 0.0)	1 ( 6.3)	0 ( 0.0)
NEUTROPHIL COUNT DECREASED	17 ( 27.9)	14 ( 17.3)	1 ( 1.3)	25 ( 6.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	4 ( 4.6)
WEIGHT DECREASED	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	3 ( 0.7)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	9 ( 10.3)
WEIGHT INCREASED	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	17 ( 4.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	6 ( 6.9)
WHITE BLOOD CELL COUNT DECREASED	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	6 ( 1.4)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	6 ( 6.9)

Body System Preferred Term	FERRIPROX (all doses)				DFO			
	1-5 years n=61 (%)	6-11 years n=81 (%)	12-15 years n=80 (%)	>=16 years n=420 (%)	1-5 years n= 0 (%)	6-11 years n=15 (%)	12-15 years n=16 (%)	>=16 years n=87 (%)
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>	8 ( 13.1)	14 ( 17.3)	17 ( 21.3)	118 ( 28.1)	0 ( 0.0)	3 ( 20.0)	4 ( 25.0)	29 ( 33.3)
ARTHRALGIA	8 ( 13.1)	9 ( 11.1)	9 ( 11.3)	75 ( 17.9)	0 ( 0.0)	0 ( 0.0)	1 ( 6.3)	8 ( 9.2)
BACK PAIN	0 ( 0.0)	6 ( 7.4)	12 ( 15.0)	72 ( 17.1)	0 ( 0.0)	1 ( 6.7)	3 ( 18.8)	25 ( 28.7)
PAIN IN EXTREMITY	0 ( 0.0)	1 ( 1.2)	4 ( 5.0)	24 ( 5.7)	0 ( 0.0)	2 ( 13.3)	1 ( 6.3)	5 ( 5.7)
<b>NERVOUS SYSTEM DISORDERS</b>	0 ( 0.0)	17 ( 21.0)	28 ( 35.0)	111 ( 26.4)	0 ( 0.0)	3 ( 20.0)	8 ( 50.0)	27 ( 31.0)
HEADACHE	0 ( 0.0)	17 ( 21.0)	28 ( 35.0)	111 ( 26.4)	0 ( 0.0)	3 ( 20.0)	8 ( 50.0)	27 ( 31.0)
<b>RENAL AND URINARY DISORDERS</b>	0 ( 0.0)	8 ( 9.9)	24 ( 30.0)	62 ( 14.8)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
CHROMATURIA	0 ( 0.0)	8 ( 9.9)	24 ( 30.0)	62 ( 14.8)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
<b>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</b>	0 ( 0.0)	1 ( 1.2)	5 ( 6.3)	9 ( 2.1)	0 ( 0.0)	0 ( 0.0)	1 ( 6.3)	6 ( 6.9)
DYSMENORRHOEA	0 ( 0.0)	1 ( 1.2)	5 ( 6.3)	9 ( 2.1)	0 ( 0.0)	0 ( 0.0)	1 ( 6.3)	6 ( 6.9)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>	2 ( 3.3)	17 ( 21.0)	32 ( 40.0)	113 ( 26.9)	0 ( 0.0)	7 ( 46.7)	7 ( 43.8)	20 ( 23.0)
COUGH	2 ( 3.3)	16 ( 19.8)	26 ( 32.5)	85 ( 20.2)	0 ( 0.0)	7 ( 46.7)	4 ( 25.0)	14 ( 16.1)
OROPHARYNGEAL PAIN	0 ( 0.0)	10 ( 12.3)	18 ( 22.5)	61 ( 14.5)	0 ( 0.0)	3 ( 20.0)	5 ( 31.3)	10 ( 11.5)

1) On-Treatment Adverse Events are coded with MedDRA Dictionary Version 13.0

2) Percentage is calculated based on the number of subjects exposed with systemic iron overload primary diagnoses in each dosing group and age category. The table is filtered for any MedDRA PT with >5% in the Ferriprox all doses or DFO columns. %Body System is calculated by the number of unique patients with PTs that appear on the report.

3) Subjects exposed to more than one Ferriprox dose are classified by their maximum dose. The age when subjects were first exposed to Ferriprox is used.

4) There are 13 subjects whose maximum dose of Ferriprox is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These Subjects are included in Ferriprox (all doses)

5) Data cutoff date: 31 Aug 2010

### 7.2.3 Special Animal and/or In Vitro Testing

Since February 28, 2009, the sponsor has completed a Segment I fertility study in rats, two dose-range-finding studies in rodents as part of an on-going carcinogenicity testing program, and two studies investigating the extent of binding and the metabolism of deferiprone in various species.

### 7.2.4 Routine Clinical Testing

Not performed.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Not performed.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not performed.

## 7.3 Major Safety Results

### 7.3.1 Deaths

In ApoPharma sponsored clinical studies, 17 deaths occurred, representing 1.3 deaths per 100 subject-years of exposure. Fourteen (14) of these deaths occurred in LA-04/06B, the compassionate use program. Subjects enrolled in that trial had failed other chelator therapy and many exhibited iron-induced toxicity prior to commencing treatment with deferiprone. Underlying diseases included thalassemia (9 subjects), myelodysplasia (3), myelofibrosis (2) thalassemia/hemoglobin E (1), Aase syndrome (1) and hereditary hemochromatosis (1). The reported causes of death were trauma (2 subjects), iron-induced cardiac disease (8), multi-organ failure (1), malignant lung tumor (1), acute myeloid leukemia (1), diarrhea (1), pleural effusion (1), adenocarcinoma (1) and intestinal obstruction (1). Only one of the deaths was considered to be possibly due to deferiprone use. The dose of deferiprone was 91-100 mg/kg/d in 3 of the patients, 50 mg/kg/d in 1 of the patients and 75 mg/kg/d in the remainder. The length of time of administration of deferiprone varied from 2 - 2681 days. These data are shown on the following table.

**Table 6.1-1: Listing of Reported Deaths in Pooled Clinical Studies**

Study ID	Subject ID	Treatment Group	Sponsor Defined Primary Diagnosis	Age at the time of Death (years)	Gender	Total Days on Study (before Death)	Days while Exposed	Days after end of Exposure (before Death)	Relationship to Study Drug	Primary Cause of Death (Preferred Term)*
LA_01	61	FERRIPROX 75 MG/KG/DAY	THALASSEMIA MAJOR	27	M	172	170	2	DOUBTFUL	CARDIAC FAILURE CONGESTIVE
LA_0208	604	FERRIPROX 75 MG/KG/DAY	THALASSEMIA MAJOR	22	M	1728	1708	20	NOT RELATED	INTERNAL INJURY
LA_04	38	FERRIPROX 75 MG/KG/DAY	THALASSEMIA MAJOR	23	F	53	48	7	DOUBTFUL	CARDIAC FAILURE CHRONIC
LA_04	39	FERRIPROX 75 MG/KG/DAY	MYELOFIBROSIS	68	M	209	180	29	NOT RELATED	MULTI-ORGAN FAILURE
LA_04	49	FERRIPROX 75 MG/KG/DAY	THALASSEMIA MAJOR	45	M	2704	2681	23	NOT RELATED	POST PROCEDURAL COMPLICATION
LA_04	98	FERRIPROX 91.2 MG/KG/DAY	THALASSEMIA MAJOR	53	F	2626	2606	20	NOT RELATED	ADENOCARCINOMA
LA_04	109	FERRIPROX 75 MG/KG/DAY AND DFO	THALASSEMIA MAJOR	39	M	157	157	0	NOT RELATED	CARDIOMYOPATHY
LA_04	114	FERRIPROX 75 MG/KG/DAY	MYELOFIBROSIS	45	F	242	242	0	NOT RELATED	CARDIAC FAILURE
LA_04	127	FERRIPROX 75 MG/KG/DAY	MYELODYSPLASIA	65	F	410	302	108	NOT RELATED	LUNG NEOPLASM MALIGNANT
LA_04	172	FERRIPROX 75 MG/KG/DAY AND DFO	TRANSFUSION DEPENDENT AASE SYNDROME	20	M	27	26	1	NOT RELATED	CARDIAC FAILURE
LA_04	207	FERRIPROX 75 MG/KG/DAY	MYELODYSPLASIA	74	M	280	267	3	NOT RELATED	ACUTE MYELOID LEUKAEMIA
LA_04	220	FERRIPROX 75 MG/KG/DAY AND DFO	THALASSEMIA MAJOR	18	M	30	29	1	NOT RELATED	CARDIAC FAILURE CONGESTIVE

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LA_04	224	FERRIPROX 100 MG/KG/DAY	MYELODYSPLASIA	72	M	753	713	40	NOT RELATED	PLEURAL EFFUSION
LA_04	240*	FERRIPROX 96 MG/KG/DAY AND DFO	THALASSEMIA MAJOR	31	M	2	2	0	NOT RELATED	ARRHYTHMIA AND CARDIAC FAILURE
LA_04	277	FERRIPROX 75 MG/KG/DAY AND DFO	THALASSEMIA MAJOR	32	F	6	5	1	POSSIBLE	CARDIOGENIC SHOCK
LA_11	107	FERRIPROX 50 MG/KG/DAY	HEMOGLOBIN E- THALASSEMIA DISEASE	33	M	148	146	2	DOUBTFUL	DIARRHOEA
LA_04	222	FERRIPROX 75 MG/KG/DAY	HEREDITARY HEMOCHROMATOSIS	53	F	343	343	0	NOT RELATED	INTESTINAL OBSTRUCTION

1) There are a total of 642 subjects systemic iron overload exposed to Ferriprox in Clinical Trials.

2) Subjects LA\_04\_41 (Cause=Hepatic Cirrhosis) and LA\_04\_199 (Cause=Unknown) died post-study withdrawal and are not included above as this information is not part of the Clinical Database.

3) Treatment Group is based on maximum dose taken. \*Coded with MedDRA Dictionary Version 13.0

4) Age at the time of Death is calculated as (Date of Death or Withdrawal - Date of Birth)/365.25, rounded down to the nearest integer.

5) Relationship to study drug based on reporter's causality assessment.

6) \*Subject LA\_04\_240 on Alternate/Combination Therapy with Ferriprox died from arrhythmia and cardiac failure 2 days after being exposed to Deferiprone. The Arrhythmia and cardiac failure were pre-treatment (with Ferriprox) events. This withdrawal is included as an SAE.

8) Data cutoff date: 31 AUG 2010

In post-marketing surveillance, the sponsor has received reports of 19 deaths since the first marketing authorization in 1999. The causes of death included agranulocytosis due to deferiprone (13 patients), cardiac failure (4), fungal infection (1) and sepsis (1). These data are shown in the following table.

**Table 6.2-1: Listing of Death reports from Postmarketing surveillance of Ferriprox**

Case ID	Age	Gender	Description of Reported Reaction	Reported Cause of Death	MedDRA Primary Preferred Term
2003AP000129	60	M	Agranulocytosis	Shock Septic	Agranulocytosis
2003AP000464	-	M	Agranulocytosis	Infection	Agranulocytosis
2003AP000465	83	F	Agranulocytosis	Sepsis	Agranulocytosis
2005AP000076	22	F	Agranulocytosis	Septic shock	Agranulocytosis
2005AP000519	20	F	Agranulocytosis	Septic shock	Agranulocytosis
2005AP001015	40	M	Agranulocytosis	Cerebral haemorrhage	Agranulocytosis
2005AP001024	34	F	Agranulocytosis	Sepsis	Agranulocytosis
2006AP000007	17	F	Agranulocytosis	Septic shock	Agranulocytosis
2006AP000139*	28	M	Severe cardiac illness	Cardiac arrhythmias	Cardiac failure
2006AP000205	40	M	Agranulocytosis	Multi-organ failure	Agranulocytosis
2006AP000252	71	F	Agranulocytosis	Sepsis	Agranulocytosis
2006AP000322	10	F	Agranulocytosis	Embolism lung	Pulmonary embolism
2007AP000425		F	Septicemia	Sepsis	Sepsis
2007AP000992	32	M	Heart failure	Cardiac failure congestive	Cardiac failure
2007AP001306	19	F	Agranulocytosis	Sepsis	Agranulocytosis
2008AP000847	12	F	Agranulocytosis	Septicaemia	Agranulocytosis
2008AP001566	40	M	Congestive heart failure	Cardiac failure congestive	Cardiac failure
2008AP003436		F	Heart failure	Cardiac failure	Cardiac failure
2009AP004595	71	F	Fungal infection	Fungal infection	Fungal infection

\* Case 2006AP000139 was not included in the ISS due to the doubtful causal relationship to Ferriprox. However, since this case was initially submitted to the Agency as possibly related it is included in this update. The narrative for this case is presented in [section 6.3.2](#).

The sponsor states that the new safety data reviewed in this submission do not alter the benefit/risk assessment of deferiprone.

**Reviewer Comments.** Deaths in the clinical trials appear to have generally been unrelated to the administration of deferiprone and were usually due to disease progression, co-morbid conditions or were unrelated. There were no deaths due to hepatic dysfunction. Most of the deaths in post-marketing reports were due to agranulocytosis, the last of which was reported in 2008. The absence of reports of death due to agranulocytosis subsequent to 2008 is believed by the sponsor to be the result of a vigorous risk management program of education of patients/physicians, the performance of weekly blood counts with immediate termination of the drug at the earliest development of neutropenia or agranulocytosis and aggressive supportive therapy when agranulocytosis is first recognized.

A review of the clinical summaries submitted by the sponsor indicates that all of the deaths were likely related to progression of the primary disease or to co-morbid conditions except for the following patient:

- 2009AP004924 (Patient #98, Study LA04).** A 53 year old patient with thalassemia who was treated with deferiprone from May, 1995 until November, 2009 was diagnosed with adenocarcinoma in the liver (believed to be metastatic). Various stains of the tumor were considered not typical for hepatocellular carcinoma but that possibility could not be excluded. There was no comment in the report regarding the presence of cirrhosis or the degree of iron deposition. The question of a primary carcinoma of the liver was not resolved.

### 7.3.2 Nonfatal Serious Adverse Events

There were 231 serious adverse reactions reported in 147/642 subjects (22.9%) treated with deferiprone in pooled clinical studies. These data are shown in the following table.

Table 4.3-1: Summary of On-Treatment Serious Adverse Events by SOC in Pooled Clinical Studies

Body System Preferred Term	FERRIPROX 50 mg/kg/d n=25 (%)	FERRIPROX 75 mg/kg/d n=407 (%)	FERRIPROX 100 mg/kg/d n=108 (%)	FERRIPROX (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with FERRIPROX n=89 (%)
SUBJECTS WITH ANY SAE	3 ( 12.0)	110 ( 27.0)	11 ( 10.2)	147 ( 22.9)	4 ( 3.4)	22 ( 24.7)
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>	0 ( 0.0)	45 ( 11.1)	8 ( 7.4)	57 ( 8.9)	1 ( 0.8)	4 ( 4.5)
NEUTROPENIA	0 ( 0.0)	28 ( 6.9)	7 ( 6.5)	39 ( 6.1)	1 ( 0.8)	4 ( 4.5)
AGRANULOCYTOSIS	0 ( 0.0)	9 ( 2.2)	2 ( 1.9)	11 ( 1.7)	0 ( 0.0)	0 ( 0.0)
LYMPHADENITIS	0 ( 0.0)	6 ( 1.5)	0 ( 0.0)	6 ( 0.9)	0 ( 0.0)	0 ( 0.0)
THROMBOCYTOPENIA	0 ( 0.0)	2 ( 0.5)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	0 ( 0.0)
LYMPHADENOPATHY	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
<b>CARDIAC DISORDERS</b>	0 ( 0.0)	8 ( 2.0)	0 ( 0.0)	17 ( 2.6)	1 ( 0.8)	9 ( 10.1)
CARDIAC FAILURE CONGESTIVE	0 ( 0.0)	3 ( 0.7)	0 ( 0.0)	7 ( 1.1)	1 ( 0.8)	4 ( 4.5)
ATRIAL FIBRILLATION	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	4 ( 0.6)	0 ( 0.0)	3 ( 3.4)
CARDIAC FAILURE	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	3 ( 0.5)	0 ( 0.0)	2 ( 2.2)
ATRIAL FLUTTER	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	1 ( 1.1)
ANGINA UNSTABLE	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
CARDIAC FAILURE CHRONIC	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
CARDIOGENIC SHOCK	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
COR PULMONALE	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
INTRACARDIAC THROMBUS	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
TORSADE DE POINTES	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
<b>EAR AND LABYRINTH DISORDERS</b>	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	1 ( 1.1)
DEAFNESS	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)

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Body System Preferred Term	FERRIPROX 50 mg/kg/d n=25 (%)	FERRIPROX 75 mg/kg/d n=407 (%)	FERRIPROX 100 mg/kg/d n=108 (%)	FERRIPROX (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with FERRIPROX n=89 (%)
VERTIGO	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
<b>GASTROINTESTINAL DISORDERS</b>	<b>1 ( 4.0)</b>	<b>7 ( 1.7)</b>	<b>0 ( 0.0)</b>	<b>8 ( 1.2)</b>	<b>0 ( 0.0)</b>	<b>0 ( 0.0)</b>
ABDOMINAL PAIN	0 ( 0.0)	4 ( 1.0)	0 ( 0.0)	4 ( 0.6)	0 ( 0.0)	0 ( 0.0)
ABDOMINAL ADHESIONS	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
COLITIS	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
DIARRHOEA	1 ( 4.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
PANCREATITIS	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>	<b>0 ( 0.0)</b>	<b>4 ( 1.0)</b>	<b>0 ( 0.0)</b>	<b>9 ( 1.4)</b>	<b>0 ( 0.0)</b>	<b>4 ( 4.5)</b>
PYREXIA	0 ( 0.0)	2 ( 0.5)	0 ( 0.0)	7 ( 1.1)	0 ( 0.0)	4 ( 4.5)
MULTI-ORGAN FAILURE	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
PAIN	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
<b>HEPATOBIILIARY DISORDERS</b>	<b>0 ( 0.0)</b>	<b>3 ( 0.7)</b>	<b>0 ( 0.0)</b>	<b>3 ( 0.5)</b>	<b>0 ( 0.0)</b>	<b>0 ( 0.0)</b>
CHOLELITHIASIS	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
HEPATIC CONGESTION	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
HEPATITIS	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
<b>INFECTIONS AND INFESTATIONS</b>	<b>0 ( 0.0)</b>	<b>21 ( 5.2)</b>	<b>2 ( 1.9)</b>	<b>34 ( 5.3)</b>	<b>0 ( 0.0)</b>	<b>10 ( 11.2)</b>
CELLULITIS	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	5 ( 0.8)	0 ( 0.0)	3 ( 3.4)
GASTROINTESTINAL INFECTION	0 ( 0.0)	3 ( 0.7)	0 ( 0.0)	3 ( 0.5)	0 ( 0.0)	0 ( 0.0)
INFECTIOUS MONONUCLEOSIS	0 ( 0.0)	3 ( 0.7)	0 ( 0.0)	3 ( 0.5)	0 ( 0.0)	0 ( 0.0)
SEPSIS	0 ( 0.0)	2 ( 0.5)	0 ( 0.0)	3 ( 0.5)	0 ( 0.0)	1 ( 1.1)
DEVICE RELATED INFECTION	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	2 ( 2.2)
DEVICE RELATED SEPSIS	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	2 ( 2.2)
PHARYNGOTONSILLITIS	0 ( 0.0)	2 ( 0.5)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	0 ( 0.0)
PNEUMONIA	0 ( 0.0)	2 ( 0.5)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	0 ( 0.0)
URINARY TRACT INFECTION	0 ( 0.0)	2 ( 0.5)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	0 ( 0.0)
ACUTE SINUSITIS	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
BACTERAEMIA	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
BACTERIAL INFECTION	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
BACTERIAL SEPSIS	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
BRONCHOPNEUMONIA	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
CORNEAL ABSCESS	0 ( 0.0)	0 ( 0.0)	1 ( 0.9)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
CYTOMEGALOVIRUS HEPATITIS	0 ( 0.0)	0 ( 0.0)	1 ( 0.9)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
GASTROENTERITIS VIRAL	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
INFLUENZA	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
MENINGITIS BACTERIAL	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
PYELONEPHRITIS	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
SERRATIA SEPSIS	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
SINUSITIS	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
STAPHYLOCOCCAL INFECTION	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
TONSILLITIS	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
UPPER RESPIRATORY TRACT INFECTION	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
VIRAL INFECTION	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
YERSINIA INFECTION	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)

Body System Preferred Term	FERRIPROX 50 mg/kg/d n=25 (%)	FERRIPROX 75 mg/kg/d n=407 (%)	FERRIPROX 100 mg/kg/d n=108 (%)	FERRIPROX (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with FERRIPROX n=89 (%)
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>	1 ( 4.0)	11 ( 2.7)	0 ( 0.0)	12 ( 1.9)	0 ( 0.0)	0 ( 0.0)
FEMUR FRACTURE	0 ( 0.0)	2 ( 0.5)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	0 ( 0.0)
ROAD TRAFFIC ACCIDENT	0 ( 0.0)	2 ( 0.5)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	0 ( 0.0)
TRANSFUSION REACTION	0 ( 0.0)	2 ( 0.5)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	0 ( 0.0)
FEMORAL NECK FRACTURE	1 ( 4.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
FOOT FRACTURE	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
FRACTURE	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
HIP FRACTURE	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
INTERNAL INJURY	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
STERNAL FRACTURE	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
THORACIC VERTEBRAL FRACTURE	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
<b>INVESTIGATIONS</b>	0 ( 0.0)	2 ( 0.5)	0 ( 0.0)	4 ( 0.6)	0 ( 0.0)	2 ( 2.2)
ARTHROSCOPY	0 ( 0.0)	2 ( 0.5)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	0 ( 0.0)
BLOOD GLUCOSE INCREASED	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	2 ( 2.2)
<b>METABOLISM AND NUTRITION DISORDERS</b>	0 ( 0.0)	4 ( 1.0)	0 ( 0.0)	9 ( 1.4)	0 ( 0.0)	5 ( 5.6)
DIABETIC KETOACIDOSIS	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	3 ( 0.5)	0 ( 0.0)	2 ( 2.2)
DIABETES MELLITUS	0 ( 0.0)	2 ( 0.5)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	0 ( 0.0)
HYPOGLYCAEMIA	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	1 ( 1.1)
DEHYDRATION	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
HYPOCALCAEMIA	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
HYPOKALAEMIA	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>	0 ( 0.0)	2 ( 0.5)	0 ( 0.0)	6 ( 0.9)	0 ( 0.0)	3 ( 3.4)
BACK PAIN	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	1 ( 1.1)
BURSITIS	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
INTERVERTEBRAL DISC PROTRUSION	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
JOINT EFFUSION	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
MUSCULOSKELETAL PAIN	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
<b>NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)</b>	0 ( 0.0)	3 ( 0.7)	0 ( 0.0)	4 ( 0.6)	0 ( 0.0)	0 ( 0.0)
ACUTE MYELOID LEUKAEMIA	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
ADENOCARCINOMA	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
LEUKAEMIA	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
LUNG NEOPLASM MALIGNANT	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
<b>NERVOUS SYSTEM DISORDERS</b>	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	1 ( 0.8)	0 ( 0.0)
ENCEPHALITIS	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
MIGRAINE	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.8)	0 ( 0.0)
<b>PSYCHIATRIC DISORDERS</b>	0 ( 0.0)	2 ( 0.5)	0 ( 0.0)	4 ( 0.6)	0 ( 0.0)	2 ( 2.2)
CONFUSIONAL STATE	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
MAJOR DEPRESSION	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
OPPOSITIONAL DEFIANT DISORDER	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
SELF INJURIOUS BEHAVIOUR	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
SUICIDAL IDEATION	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)

Body System Preferred Term	FERRIPROX 50 mg/kg/d n=25 (%)	FERRIPROX 75 mg/kg/d n=407 (%)	FERRIPROX 100 mg/kg/d n=108 (%)	FERRIPROX (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with FERRIPROX n=89 (%)
<b>RENAL AND URINARY DISORDERS</b>	1 ( 4.0)	2 ( 0.5)	0 ( 0.0)	3 ( 0.5)	1 ( 0.8)	0 ( 0.0)
RENAL COLIC	0 ( 0.0)	2 ( 0.5)	0 ( 0.0)	2 ( 0.3)	0 ( 0.0)	0 ( 0.0)
NEPHROLITHIASIS	1 ( 4.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
PYELOCALIECTASIS	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.8)	0 ( 0.0)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>	0 ( 0.0)	2 ( 0.5)	1 ( 0.9)	5 ( 0.8)	0 ( 0.0)	2 ( 2.2)
CHYLOTHORAX	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
PLEURAL EFFUSION	0 ( 0.0)	0 ( 0.0)	1 ( 0.9)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
PULMONARY CONGESTION	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
PULMONARY OEDEMA	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
RESPIRATORY DISTRESS	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
<b>SURGICAL AND MEDICAL PROCEDURES</b>	0 ( 0.0)	19 ( 4.7)	0 ( 0.0)	21 ( 3.3)	0 ( 0.0)	1 ( 1.1)
SPLENECTOMY	0 ( 0.0)	8 ( 2.0)	0 ( 0.0)	8 ( 1.2)	0 ( 0.0)	0 ( 0.0)
CHOLECYSTECTOMY	0 ( 0.0)	3 ( 0.7)	0 ( 0.0)	3 ( 0.5)	0 ( 0.0)	0 ( 0.0)
KNEE OPERATION	0 ( 0.0)	3 ( 0.7)	0 ( 0.0)	3 ( 0.5)	0 ( 0.0)	0 ( 0.0)
ADENOTONSILLECTOMY	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
CATHETERISATION VENOUS	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 1.1)
HERNIA REPAIR	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
LITHOTRIPSY	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
MENISCUS OPERATION	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
NAIL OPERATION	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
TYMPANOPLASTY	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
URETEROLITHOTOMY	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)
URETHRAL REPAIR	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	1 ( 0.2)	0 ( 0.0)	0 ( 0.0)

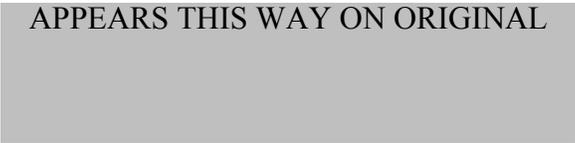
- 1) On-Treatment Serious Adverse Events are coded with MedDRA Dictionary Version 13.0
- 2) This table is based on the primary Serious Adverse Event.
- 3) Percentage is calculated based on the number of subjects exposed with systemic iron overload primary diagnoses in each dosing group.
- 4) Subjects exposed to more than one Ferriprox dose are classified by their maximum dose.
- 5) There are 13 subjects whose maximum dose of Ferriprox is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These Subjects are included in Ferriprox (all doses), where applicable.
- 6) Data cutoff date: 31 AUG 2010

For 60 of the SAEs, this led to discontinuation of deferiprone, and for 15 of the SAEs, the outcome was fatal. Seventy-eight of the SAEs were reported since the previous cut-off date of August 31, 2006. Of the 78, there were 15 episodes of neutropenia, 4 of agranulocytosis and 3 of pyrexia. Most of the other SAEs were reported in only a single patient and did not appear to be causally related to deferiprone. Sixty-one of the 78 SAEs were experienced by 27 subjects treated in study LA-04/06B (Compassionate Use Program) in which patients who could not be adequately treated with other chelators were eligible to receive deferiprone. Many of these patients had organ damage from iron overload or had co-morbid conditions.

Agranulocytosis was the most clinically important SAE, and occurred in 1.7% of patients (11/642) in clinical trials. Agranulocytosis was less common in patients with thalassemia (1.3%, 8/607 subjects) than it was in patients with non-thalassemic causes for the need for transfusion (8.6%, 3/35 subjects), including 2 with MDS and 1 with sickle cell disease.

The time of onset of agranulocytosis was 65 days to 9.2 years (median, 161 days) after commencing deferiprone therapy. The duration of agranulocytosis varied from 3 to 85 days (median, 10 days) but was longer in patients with non-thalassemic disorders (median, 19 days) compared to those with thalassemia (median, 9 days). The longest time to resolution of agranulocytosis was 21 days and there were no patients who had persistent agranulocytosis. Eight patients were treated with G-CSF. Three of the patients had developed neutropenia prior to agranulocytosis. These data are shown in the following table.

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**Table 4.3-2: Agranulocytosis episodes during Pooled Clinical Studies**

Definition	Thalassemia	Other Systemic Iron Overload Conditions	Total
No. of Events	8	3	11
No. of Patients	8	3	11
Total No. of Patients with systemic iron overload	607	35	642
% of Patients	1.3	8.6	1.7
Total Exposure (pt yrs)	1286.3	52.5	1338.8
Rate (Patients)/100 pt-yrs	0.6	5.7	0.8
Rate (Events)/100 pt-yrs	0.6	5.7	0.8
Median Age (yrs) of Patients with Agranulocytosis	10	58	11
Age (Min / Max) yrs of Patients with Agranulocytosis	4 / 18	12 / 64	4 / 64
Sex of Patients with Agranulocytosis - Male / Female	2 / 6	1 / 2	3 / 8
Median Duration of DFP Exposure for Patients with Agranulocytosis (days)	157	302	181
Range of Duration of DFP Exposure for Patients with Agranulocytosis (days)	67 / 3329	181 / 2854	67 / 3329
Median Duration (days)	9	19	10
Duration (Min / Max) days	3 / 18	16 / 85	3 / 85
Median Time to Agranulocytosis (days)	160.5	301	181
Time to Agranulocytosis (Min / Max) days	65 / 3352	140 / 567	65 / 3352
G-CSF use in Agranulocytosis Events - Yes / No / Unknown	6 / 2 / 0	2 / 1 / 0	8 / 3 / 0
Hepatitis C of Agranulocytosis Patients - Yes / No / Unknown	2 / 6 / 0	0 / 3 / 0	2 / 9 / 0
Splenectomy of Agranulocytosis Patients - Yes / No / Unknown	1 / 5 / 2	1 / 2 / 0	2 / 7 / 2

Footnote:

- 1) Clinical Studies included: LA-01, LA-02/06, LA-03, LA-04/06B, LA08-9701, LA10-9902, LA-11, LA-15, LA16-0102, LA28-CMP, LA30-0307.
- 2) Patients exposed to ApoPharma's DFP with systemic iron overload primary diagnoses are included. Planned doses for these studies range from 45 to 100 mg/kg/day.
- 3) Years of Exposure = ((End Date of Exposure - First Date of Exposure +1) - sum of interruption days)/365.25
- 4) Age is calculated as (First Exposure Date - Date of Birth)/365.25, rounded down to the nearest integer
- 5) Duration of event (days) is calculated as (Date of AE Resolution - Date of AE Onset +1), where available.
- 6) Time to Event is calculated as (Date of AE Onset - First Date of Exposure).
- 7) Median Duration of DFP Exposure for Patients with Agranulocytosis (days) calculates the years of exposure for patients with agranulocytosis.
- 8) Hepatitis C positive-reports did not provide information if the positivity for Hepatitis C refers to the presence of antibodies or the presence of the Hepatitis C virus.
- 9) GCSF=Granulocyte Colony Stimulating Factor
- 10) Data cut off date: 31AUG2010.

SAEs experienced in clinical trials and believed to be related to deferiprone included neutropenia (38 subjects, 5.9%), agranulocytosis (11, 1.7%), torsade de pointes (1, 0.2%), deafness (1, 0.2%), hepatitis (1, 0.2%), cytomegalovirus hepatitis (1, 0.2%), serratia sepsis (1, 0.2%) and the need for arthroscopy (1, 0.2%).

SAEs reported in post-marketing experience are shown in the following table.

**Table 4.4-2: Post-Marketing Serious Adverse Drug Reactions**

Body System Preferred Term	Number of Events*
<b>Blood and Lymphatic System Disorders</b>	<b>190</b>
Agranulocytosis	94
Neutropenia	96
<b>Cardiac Disorders</b>	<b>5</b>
Atrial fibrillation	1
Cardiac failure	3
Cardiac failure congestive	1
<b>Congenital, familial and genetic disorders</b>	<b>1</b>
Congenital anomaly	1
<b>Eye disorder</b>	<b>2</b>
Diplopia	1
Retinal toxicity	1
<b>Gastrointestinal disorders</b>	<b>5</b>
Abdominal pain	2
Gastric ulcer	1
Pancreatitis	1
Vomiting	1
<b>General Disorders and Administration Site Conditions</b>	<b>2</b>
Asthenia	1
Chills	1
<b>Immune system disorders</b>	<b>2</b>
Hypersensitivity	2

Body System	Number of Events*
Preferred Term	
<b>Infections and Infestations</b>	<b>4</b>
Fungal infection	1
Hepatitis infectious	1
Sepsis	1
Subcutaneous abscess	1
<b>Investigations</b>	<b>2</b>
Blood bilirubin increased	1
Aspartate aminotransferase increased	1
<b>Metabolism and Nutrition Disorders</b>	<b>1</b>
Metabolic acidosis	1
<b>Musculoskeletal and Connective Tissue Disorders</b>	<b>9</b>
Arthralgia	2
Arthritis	1
Bone pain	1
Joint Effusion	1
Muscular weakness	1
Myositis	1
Polyarthrits	2
<b>Nervous System Disorders</b>	<b>8</b>
Altered state of consciousness	1
Cerebellar syndrome	2
Convulsion	1
Headache	1
Intracranial pressure increased	2
Pyramidal tract syndrome	1
<b>Psychiatric Disorders</b>	<b>1</b>
Depression	1
<b>Skin and Subcutaneous Tissue Disorders</b>	<b>2</b>
Henoch-Schonlein purpura	1
Urticaria	1
<b>All Body System Classification Total</b>	<b>234</b>

\*Primary events presented

Data cut off: 31 AUG 2010

**Reviewer Comments.** The clinically most important adverse reaction associated with the use of deferiprone continues to be the development of agranulocytosis. This adverse reaction occurred in 1.7% of patients treated with the drug in clinical trials. It appears to be more common in patients with non-thalassemic disorders than in patients with thalassemia, perhaps because in the latter there is often a deficiency of bone marrow production and these patients may be more susceptible to an additional marrow insult caused by deferiprone. The development of neutropenia may be a herald of progression to agranulocytosis, but this is not clear. In patients who survive the episode of agranulocytosis, thus far no apparent permanent bone marrow incapacitation has been observed. No deaths due to agranulocytosis have

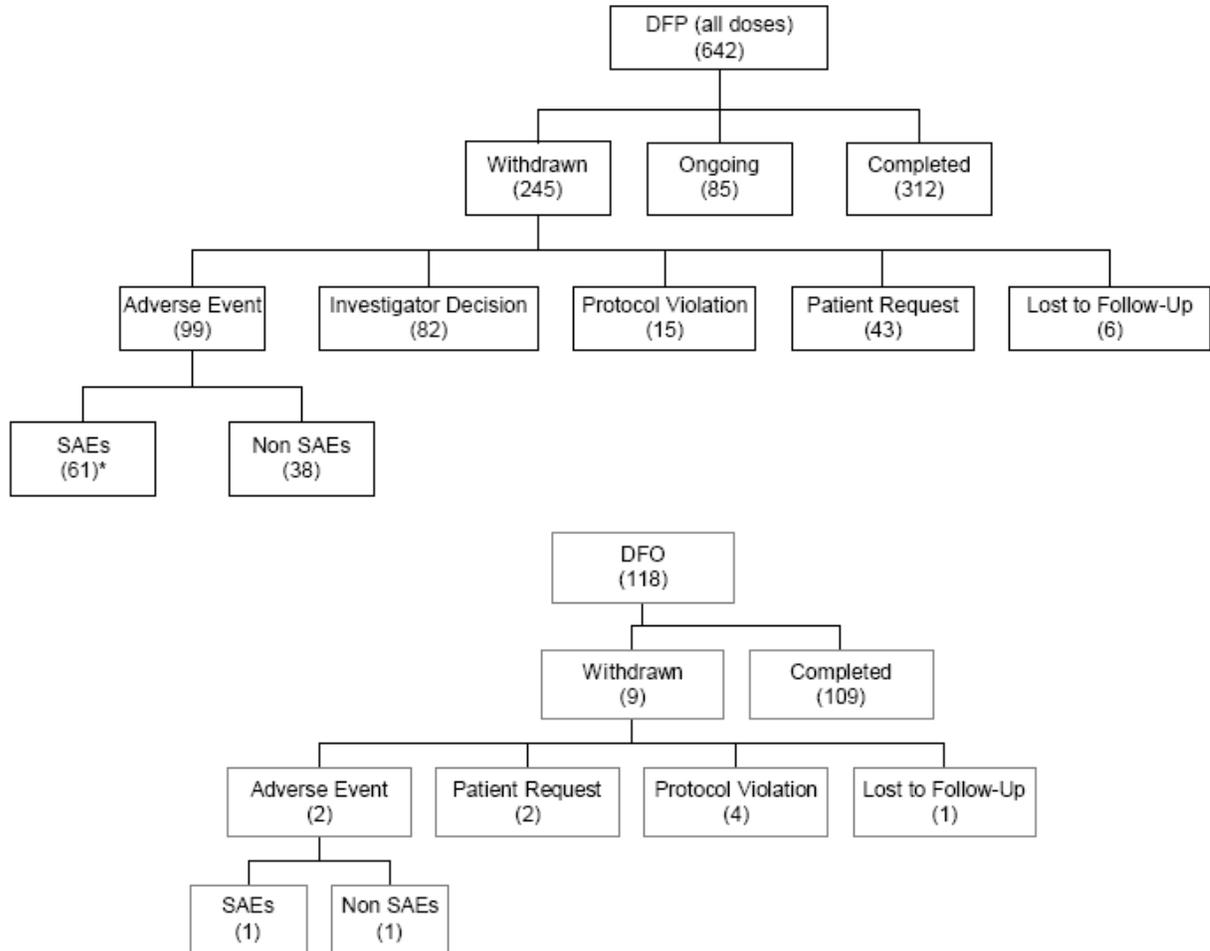
**been reported in clinical trials, but there have been 13 reported deaths due to agranulocytosis in post-marketing pharmacovigilance. The mechanism of the production of agranulocytosis has not been established.**

**Other adverse reactions associated with the use of deferiprone include gastrointestinal symptoms, arthropathy and fever. A single case of torsade de pointes has also been reported.**

### 7.3.3 Dropouts and/or Discontinuations

Of the 642 subjects enrolled in the pooled clinical studies, 312 completed the study, 245 were withdrawn and 85 were still ongoing at the cut-off date of August 31, 2010. The reasons for withdrawal from treatment and a comparison to the completion rate for patients treated with the active comparator (deferoxamine) are shown in the following figure.

**Figure 5.1-1: Disposition of Ferriprox (DFP) and DFO treated subjects in Pooled Clinical Studies from 1993 to 2010**



1) The disposition category from the last trial is displayed for subjects who participated in more than one trial.  
 2) \*Subject LA\_04\_240 on Alternate/Combination Therapy with Ferriprox died from ARRHYTHMIA and CARDIAC FAILURE 2 days after being exposed to Ferriprox. The ARRHYTHMIA and CARDIAC FAILURE were pre-treatment (with Ferriprox) events. This withdrawal is included as an SAE.  
 3)Data cutoff date: 31 AUG 2010

Of the 245 subjects withdrawn from deferiprone, 99 (15.4%) were for adverse reactions, 43 (6.7%) were at the subject’s request and 82 (12.8%) were the result of investigator decision. Most of the withdrawals (170) occurred in subjects over the age of 16 years.

**Reviewer Comments.** The rate of withdrawals from treatment compared to completion of treatment (245/312) with deferiprone is relatively high. The sponsor attributes this observation to long term treatment with deferiprone; use of a new drug; concerns about potential serious adverse reactions; use of fixed dose of deferiprone; and, availability of alternative therapy (deferoxamine). However, the sponsor does not provide an analysis of the reasons for withdrawal because of

**investigator decision or patient request. These could include lack of effect on body iron burden; reassessment of benefit/risk utility; approval of new drugs; difficulty with compliance; the development of intercurrent co-morbid conditions that lessened the potential benefit of deferoxamine; and, other unknown explanations. This rate of non-completion for a drug that requires long term administration lessens its value in patients who are expected to continue the need to be transfused.**

#### 7.3.4 Significant Adverse Events

See Page 93, Section 7.3.4 of previous review in Appendix 9.4.

#### 7.3.5 Submission Specific Primary Safety Concerns

See Page 93, Section 7.3.5 of previous review in Appendix 9.4.

### 7.4 Supportive Safety Results

#### 7.4.1 Common Adverse Events

See Page 93 - 96, Section 7.4.1 of previous review in Appendix 9.4.

#### 7.4.2 Laboratory Findings

See Pages 96 - 98, Section 7.4.2 of previous review in Appendix 9.4.

The following analytes were assessed and re-integrated with updated information:

- Alanine aminotransferase (ALT). The following tables provide the numbers of subjects with normal values for ALT at baseline whose ALT increased to  $> 2 \times$  ULN for 2 or more consecutive visits or were at those levels at the last on-treatment visit during the administration of deferiprone.

**Table 7.1-2: Summary of Subjects in Pooled Clinical Studies with ALT values within the normal range at baseline, but greater than 2, 3 or 5 times the ULN for two or more consecutive visits.**

ALT > 2 x ULN n (%)		ALT > 3 x ULN n (%)		ALT > 5 x ULN n (%)	
FERRIPROX (n = 333)	DFO (n = 73)	FERRIPROX (n = 333)	DFO (n = 73)	FERRIPROX (n = 333)	DFO (n = 73)
41 (12.31)	2 (2.74)	21 (6.31)	1 (1.37)	6 (1.80)	0 (0.00)

1) Analysis was done on subjects with normal ALT at baseline

2) Percentage is calculated based on the number of subjects with normal ALT at baseline

ALT = Alanine Transaminase; FERRIPROX = Deferiprone; DFO = Deferoxamine; NA = Not Applicable; ULN = Upper Limit of Normal Reference Range

Cut-off Date: 31AUG2010

**Table 7.1-3: Summary of Subjects in Pooled Clinical Studies with ALT values within the normal range at baseline, but greater than 2, 3 or 5 times the ULN at the last on-treatment visit.**

ALT > 2 x ULN n (%)		ALT > 3 x ULN n (%)		ALT > 5 x ULN n (%)	
FERRIPROX (n = 333)	DFO (n = 73)	FERRIPROX (n = 333)	DFO (n = 73)	FERRIPROX (n = 333)	DFO (n = 73)
23 (6.91)	3 (4.11)	10 (3.00)	0 (0.00)	1 (0.30)	0 (0.00)

1) Analysis was done on subjects with normal ALT at baseline

2) Percentage is calculated based on the number of subjects with normal ALT at baseline

ALT = Alanine Transaminase; FERRIPROX = Deferiprone; DFO = Deferoxamine; NA = Not Applicable; ULN = Upper Limit of Normal Reference Range

Cut-off Date: 31AUG2010

- Serum creatinine. Deferiprone had no clinically important effect on serum creatinine values.
- Serum zinc. After re-integration, approximately 12% of subjects who had a normal serum zinc level at baseline showed a decrease in serum zinc to below the reference range. The clinical significance of this finding is not known.
- Absolute neutrophil counts (ANC). Clinical study LA30-0307 assessed the frequency and significance of the development of ANC between  $1.0 - 1.5 \times 10^9/L$  in patients receiving deferiprone. Six of 100 subjects met this categorization. Of these, 4 had a single episode that resolved despite continued deferiprone use. One had two episodes that resolved despite continued use. One had two episodes, after which agranulocytosis developed.

**Reviewer Comments. The re-integration of laboratory data from recent safety data does not provide new insights into the types and frequencies of the adverse reactions that are associated with the use of deferiprone.**

### 7.4.3 Vital Signs

See Page 98, Section 7.4.3 of previous review in Appendix 9.4.

No new safety data for vital signs or abnormalities on physical examination are reported.

### 7.4.4 Electrocardiograms (ECGs)

See Page 98 -99, Section 7.4.4 of previous review in Appendix 9.4.

No new safety data for electrocardiograms are reported.

#### 7.4.5 Special Safety Studies/Clinical Trials

See Page 99, Section 7.4.5 of previous review in Appendix 9.4.

No studies were performed.

#### 7.4.6 Immunogenicity

See Page 99, Section 7.4.6 of previous review in Appendix 9.4.

No studies were performed.

### **7.5 Other Safety Explorations**

#### 7.5.1 Dose Dependency for Adverse Events

See above.

#### 7.5.2 Time Dependency for Adverse Events

See above.

#### 7.5.3 Drug-Demographic Interactions

See Page 99, Section 7.5.3 of previous review in Appendix 9.4.

#### 7.5.4 Drug-Disease Interactions

See Page 100, Section 7.5.4 of previous review in Appendix 9.4.

#### 7.5.5 Drug-Drug Interactions

See Page 100, Section 7.5.5 of previous review in Appendix 9.4.

## **7.6 Additional Safety Evaluations**

### **7.6.1 Human Carcinogenicity**

See Page 100, Section 7.6.1 of previous review in Appendix 9.4.

### **7.6.2 Human Reproduction and Pregnancy Data**

See Page 100 -101, Section 7.6.2 of previous review in Appendix 9.4.

In this submission, the sponsor reports that there were two pregnancies that occurred in the partners of two men who were receiving deferiprone. Both men had thalassemia. The pregnancy outcomes were normal for both pregnancies, but one of the infants was noted to have mild hypospadias. The sponsor had received notification of a third pregnancy in the partner of another person who was receiving deferiprone but there was no information regarding the outcome of that pregnancy.

### **7.6.3 Pediatrics and Assessment of Effects on Growth**

See Page 101, Section 7.6.3 of previous review in Appendix 9.4.

### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

See Page 101, Section 7.6.4 of previous review in Appendix 9.4.

## **7.7 Additional Submissions**

No additional submissions have been made.

## **8 Postmarket Experience**

See reports above.

## **9 Appendices**

### **9.1 Literature Review/References**

Provided within the Review

### **9.2 Labeling Recommendations**

See attached  
(Pages 67-73 Of this document)

### **9.3 Advisory Committee Meeting**

A meeting of the Oncology Drug Advisory Committee was held on September 14, 2011 to discuss NDA 21825. The agenda included presentations made by the sponsor and FDA, and an open public hearing. Members of the committee addressed questions to the sponsor and FDA. There was a discussion of the merits of the application. In response to the question “Is there a favorable benefit/risk profile for deferiprone in the treatment of patients in whom current chelation therapy is inadequate?”, the Committee, by a margin of 10 to 2, voted in the affirmative.

### **9.4 Review of Previous Submission (October 19, 2009) Pages 74-215 of this document**

### **9.5 Complete Response Letter (November 30, 2009) Pages 216-226 of this document**

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

## Appendix 9.4 Review of Previous Submission (October 19, 2009)

### CLINICAL REVIEW

Application Type Standard  
Application Number(s) 21825  
Priority or Standard Standard

Submit Date(s) January 28, 2009  
Received Date(s) January 29, 2009  
PDUFA Goal Date November 30, 2009

Reviewer Name(s) George Shashaty  
Review Completion Date October 19, 2009

Established Name Deferiprone  
(Proposed) Trade Name Ferriprox  
Therapeutic Class Iron Chelator  
Applicant ApoPharma

Formulation(s) Tablets  
Dosing Regimen 25 mg/kg three times daily  
Indication(s) Iron overload  
Intended Population(s) Thalassemia major

Pages 75 to 215 has been withheld as a duplicate copy of the "Clinical Review" dated October 19, 2009 which can be found in a later part of this "Clinical Review Section".

## 9.5 Complete Response Letter (November 30, 2009)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 21-825

**COMPLETE RESPONSE**

Cato Research  
Attention: Lynda Sutton  
U.S. Agent for ApoPharma, Inc.  
4364 South Alston Avenue  
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your new drug application (NDA) dated January 29, 2009, received January 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and under the Continuous Marketing Application (CMA)-Pilot 1 program, for Ferriprox<sup>®</sup> (deferiprone) 500 mg Tablet.

We acknowledge receipt of your submissions dated December 21, 2006; March 12 and 28, September 26, and December 21, 2007; March 19 and 27, June 12 and 27, September 15 and 29, October 29, and November 25, 2008; and amendments dated February 17 and 24 (2), March 5, 10 and 17 (2), May 7 and 28, June 9, 15 and 30, July 9 and 16, August 12 and 25, September 3, 9, 15, 22 and 23, October 8, 20 and 27, 2009.

We also acknowledge receipt of your amendments dated August 6 and October 13, 2009, which were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

### CLINICAL

1. The application contains insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling and lacks substantial evidence of efficacy from adequate and well-controlled investigations. Listed below are our requests for additional data, followed by a summary of the basis for these requests.
2. A decrease in the cardiac content of iron, as measured by magnetic resonance imaging (MRI) T2\* alterations, was the proposed treatment effect in the single confirmatory study intended to verify deferiprone safety and efficacy. Listed below are requests for additional information if you use this endpoint in any future regulatory submissions:

Pages 217 to 225 has been withheld as a duplicate copy of the "Complete Response Letter" dated November 30, 2009 which is located in the "Other Action Ltrs Section".

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/s/  
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GEORGE G SHASHATY  
09/16/2011

KATHY M ROBIE SUH  
09/16/2011

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DIVISION OF HEMATOLOGY PRODUCTS**

**MEDICAL OFFICER'S REVIEW**

NDA: 21825

Sponsor: ApoPharma, Inc  
200 Barmac Drive  
Toronto, Ontario M9L 2Z7

Drug name: Ferriprox (Deferiprone)

Indications: Iron Chelator

Route of Administration: Oral

Submission: New Protocol  
Responses to Information Request dated August 3, 2010

Date submitted: December 2, 2010

Review completed: December 14, 2010

Reviewer: George Shashaty, M.D.

**Background**

Deferiprone is an orally administered iron chelator that is being developed for the indication of the treatment of persons who had developed transfusion related hemosiderosis because of a chronic underlying anemia. NDA 21825 for Ferriprox (deferiprone) was submitted on January 29, 2009 and a Complete Response letter was sent to the sponsor on November 30, 2009. Since that date, there have been a number of communications between the sponsor and the Division to determine a path forward (see DAARTS entries dated January 20, March 31, April 13, August 8 and November 9, 2010). Most recently, discussions between the sponsor and the Division have focused on the possible approval for use of deferiprone restricted to patients who had failed iron reduction therapy after receiving other chelating agents. Although the Division has recommended that the sponsor provide evidence to assess the benefits/risks of deferiprone for the indication from adequate and well controlled trials, the sponsor has submitted a proposal for an analysis of data from all of the studies that it originally

submitted in support of the original NDA. In brief, this analysis, named Protocol LA36-0310, would determine the change in serum ferritin at baseline and after one year of deferiprone treatment as the primary endpoint with changes in cardiac MRI T2\* and liver iron concentration (LIC) at the same time points. A draft of this protocol, dated September 13, 2010 was submitted and reviewed, and a list of comments was forwarded to the sponsor from the Division on November 9, 2010. These comments indicated that the study could be conducted but offered no certainty to the sponsor that such a study, even if it achieved a successful conclusion as defined by the sponsor, would lead to acceptance of this analysis for the approval of deferiprone. The communication also provided recommendations that the Division believed would enhance the interpretability of the study.

The current submission includes the revision for draft Protocol LA36-0310 with a more comprehensive statistical plan.

### **Review of the Submission**

The sponsor originally submitted a PDF version of the revised protocol. The Division requested, and the sponsor subsequently submitted, an annotated version showing all changes that had been made to the draft protocol.

The revisions to the draft protocol are:

- The selection of patients from the various studies will be performed by an Independent Selection Committee rather than by employees of the sponsor.
- Patients with an improvement in serum ferritin, MRI T2\* or LIC of > 20% in the year before commencing deferiprone will not be considered to be non-responders to other chelation therapy even when the respective iron values exceed those that would usually qualify them to be selected for inclusion in the study.
- The serum ferritin closest to Month 12, rather than any serum ferritin between 9-15 months will be used, thereby reducing bias in endpoint selection.

### **Conclusions**

The revisions above are noted, and they do respond to some of our recommendations. The deficiencies noted in previous reviews of the protocol remain and were delineated in the previous response to the sponsor. These remaining deficiencies include:

- Serum ferritin measurement (the primary efficacy endpoint) is not a definitive marker for the extent of iron overload in the body, and its level is affected by variables other than the extent of body iron overload.

- The correlation between levels of serum ferritin and LIC (a more accepted measure of body iron content) is approximately 0.62 (based on studies performed in support of the approval of deferasirox).
- Since virtually all of the patients in the studies planned to be analyzed received a dose of deferiprone of 75 mg/kg/d, there are no data available regarding a dose/response relationship for the drug.
- The bar for the success of the trial is set at a low level. The sponsor will declare success if 20% of all deferiprone treated patients have a fall in serum ferritin of 20%. It is possible that patients who experience such results are not characteristic of the population likely to be treated for the indication. Also, no evidence is provided that this amount of decrease is clinically meaningful for these patients.
- For most of the studies from which the patients are to be drawn, the serum ferritin measurements were made in local laboratories, not in a central laboratory controlled or contracted by the sponsor. The same is true for measurement of LIC. This raises an issue of data integrity and technical variability among sites.
- The populations entered in the various trials were varied. In some of the trials, patients were not transfused or were minimally transfused during the time of administration of deferiprone. Such patients are likely to demonstrate sharper falls in serum ferritin than would be expected in the overall thalassemia population.
- The sponsor has all of the data for the studies which will be used in the analyses for efficacy and safety, and presumably is already aware of the outcomes for the proposed study. This may have influenced its decision on the determination of the definition of “success”.

### **Recommendations**

- The sponsor should be informed that we have noted the revisions in Protocol LA36-0310 and have no new comments to provide.
- The sponsor should refer to our previous communications regarding this proposed study and the deficiencies that remain.
- The protocol should be reviewed by Statistics and any comments they make should be forwarded to the sponsor.

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/s/  
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GEORGE G SHASHATY  
12/16/2010

KATHY M ROBIE SUH  
12/16/2010

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DIVISION OF HEMATOLOGY PRODUCTS**

**MEDICAL OFFICER'S REVIEW**

NDA: 21825

Sponsor: ApoPharma, Inc  
200 Barnac Drive  
Toronto, Ontario M9L 2Z7

Drug name: Ferriprox (Deferiprone)

Indications: Iron Chelator

Route of Administration: Oral

Submission: New Protocol  
Responses to Information Request dated August 3, 2010

Date submitted: September 13, 2010

Review completed: October 5, 2010

Reviewer: George Shashaty, M.D.

**I. Background**

NDA 21825 (Ferriprox, deferiprone) was submitted on January 29, 2009. The indication was for the treatment of persons who had developed transfusion related hemosiderosis because of a chronic underlying anemia.

Deferiprone is an orally administered iron chelator. It was originally synthesized by a researcher in Great Britain, and early clinical trials were performed by academic physicians. In the 1990s, the development of deferiprone was assumed by Ciba/Geigy, but was later abandoned because of the frequency of agranulocytosis (approximately 1% in treated patients). In the 1990s, development was assumed by the current sponsor. Over several years, working with academicians in Canada and elsewhere, the sponsor

engaged in several studies of the efficacy and safety of the use of deferiprone. Virtually all of these studies were performed in patients with thalassemia. There was concern for the validity of the data in some of the studies. In some of the studies, endpoints that were analyzed were believed not to be predictive of true clinical benefit. For some of the studies, the sponsor did not possess the primary data.

Despite these apparent deficiencies, the sponsor was granted marketing rights for deferiprone in Europe and, subsequently, in 61 countries based on the totality of the information provided by the sponsor. In most of these countries, the indication is for the treatment of patients with thalassemia and transfusion related hemosiderosis that has been inadequately treated with other available chelating agents.

The NDA was submitted in the United States on January 29, 2009 and the clinical review was done by George Shashaty (DAARTS, October 19, 2009). The submission of the NDA included a randomized controlled trial referred to as LA16-0102. In that trial, the primary endpoint was the change in cardiac iron as measured by a cardiac MRI T2\* assessment after one year of treatment with deferiprone. The comparator drug was deferoxamine, which at the time of the study was the only approved drug for the indication. Secondary endpoints included changes in cardiac ejection fraction and other assessments of cardiac function. The Agency was concerned that the primary endpoint measured was not a validated surrogate for clinical utility. The sponsor also submitted several supportive studies and a large number of references of the use of deferiprone in patients with iron overload, again almost all of whom had thalassemia as the cause of anemia for which transfusions were required. At the conclusion of the review, the Agency sent a Complete Response (CR) letter dated November 30, 2009 to the sponsor describing the deficiencies of the data submitted. In the CR letter, the Agency recommended that the sponsor perform “adequate and well-controlled” trials with deferiprone to support the application for approval of the NDA.

Subsequent to the receipt of the CR letter by the sponsor, there were several telephone and face-to-face meetings between the sponsor and the Agency to discuss potential steps that might be taken to permit the marketing of deferiprone in the United States. In one of the meetings, there was a discussion that a change in the indication for the use of deferiprone so that its approved use would be restricted to a population that had failed other chelation therapy, which is more consistent with the approved use in the rest of the world (for the treatment of transfusion related hemosiderosis that has been inadequately treated with other available chelating agents), might lead to a consideration for approval (see minutes of April 5, 2010 meeting).

On June 21, 2010, the sponsor submitted a draft for Protocol LA36-0310 (A Clinical Trial to Evaluate the Efficacy of Deferiprone in Patients for Whom Previous Chelation Therapy Has Been Inadequate by Analysis of Data from Clinical Studies of Deferiprone) along with a discussion of the rationale for performing the study. The study proposed to use data from a number of the extant studies previously submitted to the NDA and other studies performed by the sponsor to analyze changes in serum ferritin after treatment with deferiprone in such patients. I reviewed the submission (see George Shashaty, DAARTS

dated July 12, 2010) and an Information Request letter was sent to the sponsor on August 3, 2010.

This submission is the sponsor's response to the IR letter.

### **Review of Submission**

The sponsor has submitted:

- Responses to comments made by the Division in its letter to the sponsor dated August 3, 2010
- Protocol for Study LA36-0310
- Six literature references

For ease of review, I have pasted below the original comments from our August 3, 2010 letter to the sponsor in numerical order, and have summarized the sponsor's response following each comment.

1. The title of the protocol suggests that the indication may apply to all patients with transfusional iron overload. Virtually all the patients studied in your studies had thalassemia as the cause of anemia for which transfusions were required. Unless there are data supplied for patients with other causes of chronic anemia and the need for transfusion therapy (sickle cell disease, myelodysplastic syndrome, aplastic and other anemia), the indication should be restricted to patients with thalassemia.
  - The sponsor believes that, regardless of the particular underlying chronic anemia, all patients with iron overload due to transfusion have similar iron-mediated organ dysfunction. They assert that, therefore, the fact that the overwhelming majority of patients studied in the trials that they propose to analyze had thalassemia should not restrict the use of deferiprone to only patients with thalassemia and iron overload. In its proposed protocol (LA36-0310) to analyze data from already submitted clinical studies of deferiprone to evaluate efficacy in refractory patients, the sponsor plans to include patients regardless of underlying anemia.
2. In regard to serum ferritin, while it is believed that levels in excess of 2500 mcg/L are associated with a worse outcome in patients with thalassemia compared to in patients with a level less than 2500 mcg/L, there are no data that a 20% decrease in serum ferritin confers any clinical benefit for a patient (for example, decreasing the serum ferritin from 5000 mcg/L to 4000 mcg/L). Yet this change would be considered a success for a patient treated with deferiprone.
  - The sponsor asserts that practical and ethical issues attendant upon a study to evaluate the clinical benefit of any nominal improvement in any measure of iron overload (serum ferritin, liver iron concentration, cardiac MRI T2\*) are likely the main reasons for the absence of such data. Nonetheless, the sponsor believes that the closer the iron overload parameters are to the normal reference values, the lower the risk of iron toxicity. The sponsor states that it will use a  $\geq 20\%$

- decrease in serum ferritin as a reasonably meaningful response in the planned protocol (LA36-0310) and states that they have conferred with leading U.S. clinicians in the field during the development of the protocol.
3. In regard to liver iron concentration (LIC), your use of the results of deferasirox Study 0107 [The proposed 20% reduction in SF or MRI T2\* is based on the 17% reduction in LIC from baseline (from 14.1 to 11.7 mg Fe/g dw) observed during therapy with deferasirox in the pivotal study 0107] as a comparator does not take into account the fact that persons in Study 0107 were initially dosed based on baseline LIC, some done by superconducting quantum interference device (SQUID) which is known to underestimate the LIC, and were therefore given a dose that was less than what is now known to be therapeutic. Additionally, as with other chelators, those with higher body iron burdens tend to be more responsive to chelator therapy compared to those with a lesser body iron burden. Currently, it is believed that patients with LIC < 7 mg Fe/g dw are not generally subject to the adverse effects of iron toxicity in most body organs. The clinical significance of a decrease of  $\geq 20\%$  in LIC is not known.
    - A decline of  $\geq 20\%$  in LIC represents a meaningful improvement in iron burden. This would be particularly true for patients who have not responded to other iron chelators. Additionally, most of the patients treated with deferiprone received a fixed dose of 75 mg/kg/d, which may be less than the most optimal dose.
  4. In regard to cardiac MRI T2\*, as was the problem with the data provided in the Study LA 16-0101, we are not aware of any data that show that an increase in T2\* of 20% or greater in a patient with a baseline T2\* of < 20 ms has any clinically meaningful significance.
    - The sponsor acknowledges that there are no studies evaluating the clinical benefit of any nominal improvement in any measure of iron overload. Nevertheless, the sponsor believes that an increase in cardiac MRI T2\* of  $\geq 20\%$  is a meaningful measure of improvement in iron overload. The sponsor cites the non-invasiveness of the cardiac MRI T2\* measurement and its “clinically recognized worldwide” use for evaluating patients.
  5. You will claim success for any patient whose defined improvement occurs in ANY of these variables, rather than in ALL of the variables (for example, a fall in serum ferritin would be a success even if the LIC were rising and the T2\* were falling in the same patient). Such inconsistencies among the findings for the efficacy parameters among and within patients would weaken the persuasiveness of the results.
    - The sponsor concurs with our statement that improvement in one parameter and worsening in another would compromise evidence of overall treatment success of deferiprone, but excepts cardiac MRI T2\*, which it believes is the most predictive parameter of cardiac disease and survival. The choice of a change in serum ferritin as the primary efficacy endpoint was based on the data that were available for conducting the analysis requested by the Agency and the sponsor continues to propose serum ferritin as the primary endpoint and will assess LIC and MRI T2\* to determine success when using other measures to assess patients’ response.

6. The protocol does not state the length of treatment time nor the rate of fall in serum ferritin (or LIC or T2\* for that matter) that the person must have experienced while receiving other chelation therapy before being considered a failure on that therapy. For instance, if the patient had been receiving other chelation therapy for nine months and the serum ferritin had fallen from 9000 mcg/L to 3000 mcg/L, that person could be considered to be a failure and would be eligible to be enrolled in the study even though there had clearly been some response to therapy.
  - The length of time that a patient would have to have been treated with another chelator before failure was declared may not be possible to be gleaned from the data available from some of the studies that the sponsor intends to analyze because such data may not be available. Nonetheless, for patients for whom such data are available, an improvement of  $\geq 20\%$  during a year of other chelator therapy would exclude such patients from being included in the corresponding measure. The analysis will be designed to verify that those patients with more than one baseline serum ferritin values responded to deferiprone in a manner similar to those with a single baseline value.
7. The dose of deferoxamine that the patient may have been receiving (20-40 mg/kg/day) when declared to be a failure appears to be too low to make that declaration. Although the label for deferoxamine states that the dose is 20-40 mg/kg/day, in practice, the dose administered often is increased to up to 50 mg/kg/day if adverse reactions are not encountered.
  - The sponsor does not believe that criticism should be directed at physicians for their decisions regarding the dosing of other chelators since it is likely that such dosing was determined based on the best interests of the patients treated.
8. This is a retrospective analysis of data already accumulated. There must be rigid rules in the protocol that spell out the exact methods for eliminating bias in the study.
9. To help ensure objectivity and minimize bias, there will need to be a separate group to review the data for eligibility to enroll in the trial and another group to analyze the data for efficacy and safety. Data cannot be shared between the two groups.
  - Patient selection for inclusion in the analysis will be performed by Clinical Data Management at ApoPharma and the Biostatistics group at ApoPharma will subsequently assess the serum ferritin, LIC and cardiac MRI T2\* values captured during treatment with deferiprone for up to one year for efficacy. The proposed treatment success criteria are objective and the determination of response will be performed by a computer program. The complete dataset, the SAS program for patient selection, the corresponding dataset and the SAS program for determination of responders will be submitted with the study results.
10. For many of the studies referenced to be included in the study, there did not seem to be patients who were commenced on deferiprone because of failure while receiving another chelation agent. You must use the utmost care in adhering to the inclusion/exclusion criteria established for the study.

- The evaluation of deferiprone as a second line treatment for transfusional iron overload limits the analysis of data from studies in which the original purpose was to evaluate the efficacy and safety of deferiprone or to compare the efficacy of deferiprone with that of deferoxamine. Patient enrollment into the proposed study will be based on inclusion/exclusion criteria that will have been pre-established and agreed to with the Agency.
11. The draft protocol that was submitted contains only limited statistical information. Submit a protocol with a detailed statistical analysis plan which includes detailed sample size justification and detailed subgroup analysis plans. Also provide detailed strategy and justifications for reviewing data from multiple retrospective studies to reduce bias.
- The proposed protocol contains a more detailed statistical analysis plan.
12. Keep missing data to a minimum. Address the missing data in the primary analysis. Provide a justification for your choice of LOCF imputation or any other intended method of imputation. Perform sensitivity analyses that evaluate the limitations of the data.
- In regard to minimization of missing data, the sponsor is using the imputation method of last observation carried forward (LOCF) because it is computationally simple with no subjective assessments involved, is easy to understand and provides a conservative estimate of the treatment success rate for the proposed treatment success criteria.

Protocol for Study LA36-0310

**Objective**

The objective of the study is to evaluate the efficacy of the oral administration of deferiprone in the treatment of iron overload in patients in whom previous chelation has failed. Chelation failure is defined as iron accumulation above a boundary level, defined by high serum ferritin or LIC or low cardiac MRI T2\* levels. Success is defined by stated differences in these measures of iron overload after treatment with deferiprone for approximately one year.

**Design**

This is a retrospective analysis of data derived from multiple studies (see Appendix 1), some controlled and some uncontrolled, in patients who mostly had an underlying diagnosis of beta thalassemia and transfusional iron overload. From these studies, the sponsor will extract those patients who were considered to have failed to improve their iron overload status while receiving previous chelation therapy.

**Endpoints**

The primary endpoint is the change in serum ferritin from baseline to the end of the treatment period of one year ( $\pm$  3 months of the anniversary date). Success for a particular patient will be declared if there is a decrease in serum ferritin of at least 20% compared to baseline. Success for the entire study will be declared if a successful outcome is observed in at least 20% of treated patients.

Secondary endpoints are changes in cardiac MRI T2\* and LIC from baseline to the end of the treatment period. Success for a particular patient will be declared if there is a decrease in LIC or an increase in MRI T2\* of at least 20% compared to baseline.

The definitions of success are shown in the following table.

**Table 2. Definition of Successful Chelation Therapy**

Primary endpoint	
• <b>Based on Serum Ferritin</b>	
Serum Ferritin at Baseline	Success
>2,500 µg/L	A ≥20% decline in serum ferritin from baseline within 1 year of Ferriprox therapy.
Secondary endpoints	
• <b>Based on Liver Iron Concentration (LIC)</b>	
LIC at baseline	Success
>7 mg Fe/g dw	A ≥20% decline in LIC from baseline within 1 year of Ferriprox therapy
• <b>Based on Cardiac Iron Concentration (as assessed by MRI T2*)</b>	
MRI T2* at baseline	Success
<20 ms	A ≥20% increase in MRI T2* from baseline within 1 year of Ferriprox therapy

dw = dry weight; LIC = liver iron concentration

- a The proposed ≥20% reduction in SF or LIC is based on the understanding that it would mean a drop of a minimum of 500 µg/L or 1.4 mg Fe/g dw, respectively. Those changes represent a meaningful improvement in the iron burden based on the experience with other chelators.

### Data to be collected and analyzed

Data for the study is to be collected from the 12 clinical studies that were conducted to support NDA 21825 (see Appendix 1) and will include data from completed study LA30-0307 and the ongoing compassionate use programs LA28-CMP and LA04/06B updated to a new cut-off date of May 11, 2010. Patient selection will be performed by Clinical Data Management at ApoPharma and will be based on the inclusion/exclusion criteria established in the protocol. The Biostatistics group at ApoPharma will then assess the serum ferritin, LIC and MRI T2\* values in this cohort of patients treated with deferiprone. The number of patients who achieve the criteria for success and the success rate will be determined.

Case Report Forms will not be created for this study. Case Report Forms were collected and processed as per each protocol and clinical study report.

### Patients

The study population will comprise patients who have failed on standard chelation therapy based on the following inclusion/exclusion criteria.

- Inclusion criteria (all must be met):
  - Had been receiving standard chelation therapy
  - Met one or more of the following measures of iron overload:
    - Serum ferritin > 2500 µg/L
    - Cardiac MRI T2\* < 20 ms
    - LIC > 7 mg Fe/g dw
- Exclusion criteria

- Naïve to iron chelation therapy
- Selected for study but never received deferiprone
- No data available for serum ferritin, LIC or MRI T2\* either while receiving standard chelation therapy or after initiation of deferiprone

## Statistics

Demographics, primary disease and prior iron chelation therapy will be summarized using descriptive statistics and frequency tables. For patients with more than one value for a measure of iron overload, the last value prior to the start of deferiprone treatment will be the baseline value. Patients in whom there was a  $\geq 20\%$  improvement in any of those measures within the year of previous chelation therapy will not be considered treatment failures and will not be included in the analyses.

Efficacy analyses for the primary and secondary endpoints are as shown in the sponsor's Table 2 reproduced above.

The last observation carried forward (LOCF) method will be used for data imputation as follows:

- For subjects who switched from deferiprone to another chelator, the data after the switch of therapy will be excluded, and the LOCF before the switch will be carried forward to either 1 year of therapy as defined in the protocol or the study cut-off point that is specified above.
- For subjects who stopped study treatment prematurely, data collected within 3 months after medication termination will be included, and the worst value of the LOCF or any measure obtained in the 3 month period will be used as the final result.
- For subjects who missed a visit or had an insufficient sample for a particular measurement, the last observation before the missing observation will be carried forward.

Analysis of LIC will be conducted only on those patients for whom both baseline and end-of-study measurements were made by the same technique.

The success or failure for each efficacy endpoint will be calculated based on the criteria in Table 2 above. If the lower limit of the 95% confidence interval of the observed success rate based on normal approximation is greater than 20%, the therapy will be considered successful for that particular measure. The final assessment of treatment success will be based upon the success rate for serum ferritin.

There will be subgroup analyses for patients based on:

- Single versus multiple serum ferritin values prior to commencement of deferiprone therapy

- Comparison of patients who experienced  $\geq 20\%$  decline in serum ferritin on previous chelation therapy to those with  $\geq 20\%$  decline in serum ferritin while receiving deferiprone

There will be a sensitivity analysis to support the LOCF method of imputation for missing efficacy data.

There are no sample size calculations since the analyses are to be performed on the extant data.

### **Conclusions and Recommendations**

The sponsor has responded to the issues raised by us in regard to the study that they believe should be sufficient to provide data to evaluate the efficacy and safety of the use of deferiprone in patients with transfusion dependent iron overload who have not been adequately treated with currently available iron chelation therapy, which they believe should lead to the approval of the drug for the indication. The proposed study is virtually identical to the one that the sponsor previously submitted, and the determination of efficacy continues to be based upon measurement of serum ferritin. Additional measures to be evaluated include assessment of iron in the liver and in the heart.

The proposal continues to be far from optimal for us to evaluate the sufficiency of the data to determine the safety and efficacy of deferiprone, but it appears to be the most that the sponsor is willing to provide. Problems with the proposal include:

- Serum ferritin measurement (the primary efficacy endpoint) is not a definitive marker for the extent of iron overload in the body, and its level is affected by variables other than the extent of body iron overload.
- The correlation between levels of serum ferritin and LIC (a more accepted measure of body iron content) is approximately 0.62 (based on studies performed in support of the approval of deferasirox).
- Since virtually all of the patients in the studies planned to be analyzed received a dose of deferiprone of 75 mg/kg/d, there are no data available regarding a dose/response relationship for the drug.
- The bar for the success of the trial is set at a low level. The sponsor will declare success if 20% of all deferiprone treated patients have a fall in serum ferritin of 20%. It is possible that patients who experience such results are not characteristic of the population likely to be treated for the indication. Also, no evidence is provided that this amount of decrease is clinically meaningful for these patients.
- The 12 month measurement of serum ferritin allows for the observation to have actually been performed anywhere between 9 and 15 months of deferiprone treatment, so that the sponsor may select the value most favorable to its analysis.
- For most of the studies from which the patients are to be drawn, the serum ferritin measurements were made in local laboratories, not in a central laboratory

- controlled or contracted by the sponsor. The same is true for measurement of LIC. This raises an issue of data integrity and technical variability among sites.
- The populations entered in the various trials were varied. In some of the trials, patients were not transfused or were minimally transfused during the time of administration of deferiprone. Such patients are likely to demonstrate sharper falls in serum ferritin than would be expected in the overall thalassemia population.
  - The sponsor has all of the data for the studies which will be used in the analyses for efficacy and safety, and presumably is already aware of the outcomes for the proposed study. This may have influenced its decision on the determination of the definition of “success”.

For the reasons stated above, I believe that the proposed study would not provide data that would meet the Agency’s standards for the evaluation of the efficacy and safety of the use of deferiprone for patients with transfusional hemosiderosis related to chronic anemias.

However, in view of the relatively restricted indication (particularly if limited in the label to patients with thalassemia, who were the overwhelming majority of studied patients), it might be possible to consider re-examining the “total information” available about the value of deferiprone if the sponsor analyzes that effect of treatment with deferiprone on changes in serum ferritin in patients inadequately treated with other available iron chelating agents. It is true that: for thalassemia patients at least, the most common cause of death is cardiac impairment from iron deposition and the use of deferoxamine has chronologically been associated with increasing longevity; that there are patients who appear to be inadequately treated with deferoxamine or deferasirox; and that the availability of another iron chelator might improve morbidity and mortality in these latter patients. Additionally, deferiprone is licensed in more than 60 countries worldwide, including the European Union (although peculiarly not in Canada where its sponsor has its headquarters), and its use over the last decade has not caused a flood of deaths or unexpected serious adverse reactions. The Thalassemia Foundation has repeatedly petitioned the Agency to approve the drug despite its full awareness of the risk of the development of agranulocytosis (1-5%) induced by deferiprone. The negative consequences of agranulocytosis may be amenable to control by a strict enforcement of periodic blood count determinations. Finally, the sponsor’s proposed study is in response to a suggestion by the Agency (April 5, 2010 meeting) that the sponsor consider an indication in a population of persons whose risks of morbidity/mortality were high and who had no other alternatives to which to turn.

Therefore, the response of the Division to the sponsor should be based on a consensus determination of the value of the sponsor’s proposal.

Also, the Statistics group should review the proposed protocol and statistical analysis plan and offer any recommendations that might improve its utility.

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## Appendix 1

Table 1. Listing of Studies Used to Gather Data to Evaluate the Efficacy of Deferiprone in Patients with Iron Overload for Whom Previous Chelation Therapy Has Been Inadequate.

Number	Title	Location	Number of Subjects: Entered/Completed	Study Type	Primary Objective	Available Efficacy Measurements for Analysis*		
						Serum Ferritin	LIC	MRIT2*
LA-01	Randomized Trial of L1 and Deferoxamine in Thalassemia Major	Canada	DFP: 35/27 DFO: 36/30	Randomized, open-label, active-controlled	To compare the relative effectiveness and safety of DFP and DFO therapy, as reflected by the ability of each chelator to achieve net negative iron balance, reduce tissue iron stores, and reduce body iron stores	√	√	
LA-02/06	Trial of APO-66 (Deferiprone) in Thalassemia/Maintenance Study Protocol of Deferrum™ (Ferriprox) for Subjects with Thalassemia who Complete Apotex Protocol LA-02	United States, Italy	DFP: 187/70	Open-label, uncontrolled	To monitor long-term safety and effectiveness of a fixed dose of deferiprone	√		
LA-03	The Long Term Efficacy and Safety of Deferiprone in Subjects with Thalassemia	Canada	DFP: 29/25	Open-label, uncontrolled, compassionate use	To assess the long-term efficacy and safety of DFP in patients with thalassemia and iron overload	√	√	
LA-04/06B	Compassionate-use of Deferiprone (L1) in Subjects with Iron Overload	Canada, Italy, United States	DFP: 168/23	Open-label, uncontrolled, compassionate use	To provide patients with thalassemia or other chronic iron overload conditions unable or unwilling to take DFO with an alternative treatment to control iron overload	√	√	√
LA08-9701	Safety and Efficacy of Alternating Deferoxamine and Deferiprone compared with Deferoxamine Alone in the Treatment of Iron Overload in Thalassemia Subjects	Italy, Greece	Alternating DFP and DFO: 29/29 DFO: 30/30	Randomized, open-label, parallel, active-controlled	To evaluate efficacy and safety of alternating use of DFP and DFO compared with current standard therapy with DFO in treatment of iron overload	√	√	

Number	Title	Location	Number of Subjects: Entered/Completed	Study Type	Primary Objective	Available Efficacy Measurements for Analysis*		
						Serum Ferritin	LIC	MRIT2*
LA-11	Efficacy and Safety of Deferiprone (L1) in $\beta$ -Thalassemia/Hemoglobin E Diseases Subjects in Thailand	Thailand	DFP: 24/16	Open label, uncontrolled	To study the efficacy and toxicity of DFP in patients $\beta$ -thalassemia/Hb E diseases in Thailand	√		
LA-12-9907	Retrospective Assessment of Heart Failure and Survival During Iron Chelation with Deferiprone or deferoxamine in Subjects with Transfusion-Dependent $\beta$ -Thalassemia	Italy	DFP: 54 DFO: 75  The study assessed existing data so study completion or withdrawal was not defined.	Open-label, parallel, longitudinal, active-controlled	To evaluate incidence of cardiac disease and survival in subjects treated with DFP compared with DFO over the same time period	√	√	
LA15-0002	Safety and Efficacy of Ferriprox™ for the Treatment of Iron Overload in Subjects with Transfusion-dependent Thalassemia in Iran	Iran	DFP: 29/26	Open label, uncontrolled	To monitor the efficacy and safety of DFP for the treatment of iron overload in subjects with transfusion-dependent thalassemia, as reflected by: serum ferritin concentrations the occurrence of AEs	√		
LA16-0102	Randomized Trial Comparing the Relative Efficacy of Deferiprone to that of Deferoxamine in Removing Excess Cardiac Iron in Thalassemia Major Subjects	Greece, Italy	DFP: 29/27 DFO: 32/29	Randomized, open-label, active controlled	To determine whether orally administered Ferriprox® (deferiprone) exhibits superior efficacy in removing excess iron from the heart compared to that of standard subcutaneous infusions of Desferal® (deferoxamine), as reflected by Magnetic Resonance Imaging T2-star (MRI T2*) assessments of the heart in subjects treated with either chelator	√	√	√
Borgna-Pignatti et al. (2006) <sup>9</sup>	Cardiac Morbidity and Mortality in Deferoxamine- or Deferiprone-treated Patients with Thalassemia Major	Italy	DFP: 157 DFO: 359	Retrospective, natural history	To compare the occurrence of cardiac disease in patients treated only with DFO to those whose therapy was switched to DFP during the period of observation, from 31 JAN 1995 to 31 DEC 2003	√		

Number	Title	Location	Number of Subjects: Entered/Completed	Study Type	Primary Objective	Available Efficacy Measurements for Analysis*		
						Serum Ferritin	LIC	MRIT2*
LA28-CMP	The compassionate use/named patient program of Ferriprox oral solution in iron-overloaded pediatric patients with transfusion-dependent anemias	Egypt, Malaysia, Singapore	DFP: 83/62 (72 subjects previously enrolled in LA-30)	Multi-center, open label, single treatment, uncontrolled, compassionate use/named patient basis program	To provide treatment with Ferriprox oral solution to iron-overloaded pediatric patients with transfusion-dependent anemias for whom deferoxamine is contraindicated or inadequate.	√		
LA-30	24-week open label, uncontrolled study of the safety and efficacy of Ferriprox (deferiprone) oral solution in iron-overloaded pediatric patients with transfusion-dependent anemia	Egypt, Indonesia, Malaysia	DFP: 100/95	Open label, uncontrolled	To assess the safety of Ferriprox oral solution for the treatment of iron overload in pediatric patients with transfusion-dependent anemia.	√		

Data cut off: 11 MAY 2010

AE = adverse event; MRI T2\* = magnetic resonance imaging T2\*; DFO = deferoxamine; DFP = deferiprone; LIC = liver iron concentration.

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/s/

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GEORGE G SHASHATY  
10/18/2010

KATHY M ROBIE SUH  
10/18/2010

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DIVISION OF HEMATOLOGY PRODUCTS**

**MEDICAL OFFICER'S REVIEW**

NDA: 21825

Sponsor: ApoPharma, Inc  
200 Barnac Drive  
Toronto, Ontario M9L 2Z7

Drug name: Ferriprox (Deferiprone)

Indications: Iron Chelator

Route of Administration: Oral

Submission: New Protocol

Date submitted: June 21, 2010

Review completed: June 29, 2010

Reviewer: George Shashaty, M.D.

**I. Background**

NDA 21825 (Ferriprox, deferiprone) was submitted on January 29, 2009. The indication was for the treatment of persons who had developed transfusion related hemosiderosis because of a chronic underlying anemia.

Deferiprone is an oral iron chelator. It was originally synthesized by a researcher in Great Britain, and early clinical trials were performed by academic physicians. In the 1990s, the development of deferiprone was assumed by Ciba/Geigy, but was later abandoned because of the frequency of agranulocytosis (approximately 1% in treated patients). In the 1990s, development was assumed by the current sponsor. Over several years, working with academicians in Canada and elsewhere, the sponsor engaged in several studies of the efficacy and safety of the

use of deferiprone. Virtually all of these studies were performed in patients with thalassemia. There was concern for the validity of the data in some of the studies. In some of the studies, endpoints that were analyzed were believed not to be predictive of true clinical benefit. For some of the studies, the sponsor did not possess the primary data.

Despite these apparent deficiencies, the sponsor was granted marketing rights for deferiprone in Europe and, subsequently, in 61 countries based on the “totality” of the information provided by the sponsor. In most of these countries, the indication is for the treatment of patients with thalassemia and transfusion related hemosiderosis that has been inadequately treated with other available chelating agents.

The NDA was submitted in the United States on January 29, 2009 and the clinical review was done by George Shashaty (DAARTS, October 19, 2009). The submission of the NDA included a single randomized controlled trial. In that trial, the primary endpoint was the change in cardiac iron as measured by a cardiac MRI T2\* assessment after one year of treatment with deferiprone. The comparator drug was deferoxamine, which at the time of the study was the only approved drug for the indication. Secondary endpoints included changes in cardiac ejection fraction and other assessments of cardiac function. The Agency was concerned that the primary endpoint measured was not a validated surrogate for clinical utility. The sponsor also submitted several supportive studies and a large number of references of the use of deferiprone in patients with iron overload, again almost all of whom had thalassemia as the cause of anemia for which transfusions were required. At the conclusion of the review, the Agency sent a Complete Response (CR) letter to the sponsor describing the deficiencies of the data submitted. In the CR letter dated November 30, 2009, the Agency recommended that the sponsor perform “adequate and well-controlled” trials with deferiprone to support the application for approval of the NDA.

Subsequent to the receipt of the CR letter by the sponsor, there were several telephone and face-to-face meetings between the sponsor and the Agency to discuss potential steps that might be taken to permit the marketing of deferiprone in the United States. In one of the meetings, there was a discussion that a change in the indication for the use of deferiprone so that its approved use would be restricted to a population that has failed other chelation therapy, which is more consistent with the approved use in the rest of the world (for the treatment of transfusion related hemosiderosis that has been inadequately treated with other available chelating agents), might lead to a consideration for approval.

This submission is the sponsor’s response to the discussion described above.

## **II. Review of the Submission**

In addition to the cover letter, the submission consists of the following two documents:

- A Study to Evaluate the Efficacy of Deferiprone in Patients with Iron Overload for Whom Standard Chelation Therapy Has Been Inadequate - Based on an Analysis of Data from Clinical Studies of Deferiprone: Background, Definitions and Criteria
- Clinical Study Protocol. LA36-0310. A Clinical Trial to Evaluate the Efficacy of Deferiprone in Patients for Whom Previous Chelation Therapy Has Been Inadequate by Analysis of Data from Clinical Studies of Deferiprone

In the first document (7 pages), the sponsor states that there are no specific guidelines as to what constitutes failure of a previous chelation therapy, and that it has reviewed the literature and consulted experts in the field to assist in the development of criteria that could be used to establish the efficacy and safety of deferiprone in such a population. Using these criteria, the sponsor will review its database of all studies of deferiprone to identify patients who had an inadequate outcome after previous chelation therapy, evaluate the response of such patients to deferiprone, analyze the data according to a predefined statistical plan and submit the report to FDA as the primary efficacy and safety study for the NDA.

Based on these considerations, failure of standard therapy will be defined as a single measure of any of the following:

- A serum ferritin > 2500 µg/L while receiving standard chelation therapy.
- A cardiac MRI T2\* < 20 ms while receiving standard chelation therapy.
- A liver iron concentration (LIC)  $\geq$  (b)(4) mg Fe/g dw while receiving standard chelation therapy.

Patients will not be considered to have failed standard therapy for either of the following reasons:

- Development of a chelator-associated adverse reaction.
- Failure of compliance.

All studies conducted by the sponsor will be analyzed to identify patients who meet the inclusion criteria. The therapeutic dose of deferoxamine will be considered to be 20-40 mg/kg/day given subcutaneously and for deferasirox will be considered to be 20-40 mg/kg/d orally. Data on treatment with these two chelators are to be obtained from the medical history as reported in the case report form. Data from the Borgna-Pignatti study will be included as well. Data on the dose and duration of chelator therapy will be provided whenever possible.

Chelation therapy with deferiprone will be considered “successful” if any of the primary or secondary endpoints are achieved.

For deferiprone to be considered to be effective, the various observed reductions would need to be demonstrated in at least 20% of the patients who failed on

standard chelation therapy for that measure. The Statistical Analysis Plan is presented in the draft protocol.

### **Draft Protocol**

The second submitted document is a draft protocol of the proposed study. It is dated June 21, 2010. The protocol is to be performed in accordance with Good Clinical Practices and the Declaration of Helsinki.

### **Objective**

The objective of the study is to evaluate the efficacy of the oral administration of deferiprone in the treatment of iron overload in patients in whom standard chelation has failed.

### **Study Design**

Data for the study will be provided from the studies that were conducted and submitted in support of the original NDA (see Appendix 1 for a table of studies).

### **Study Population**

The study population will comprise patients enrolled in the 12 clinical trials listed in Appendix 1 who had failed on standard chelation therapy. The sponsor does not state the number of patients who will be enrolled.

Inclusion criteria are:

- Patient had been receiving standard chelation therapy in accordance with approved prescribing information.
- Patient had one of the following features of increased iron overload:
  - Serum ferritin > 2500 µg/L, or
  - Cardiac MRI T2\* < 20 ms, or
  - LIC ≥ <sup>(b) (4)</sup> mg Fe/g dw

Exclusion criteria are:

- Patient was naïve to iron chelation therapy
- Patient was selected for study but never received deferiprone

- Patient lacked data at baseline or end of study for serum ferritin, LIC or cardiac MRI T2\*

### Efficacy

The following table defines successful chelation therapy. The achievement of any of the primary or secondary endpoints is counted as a success for statistical purposes. Note that the observed change may occur at any time during the one year period of treatment with deferasiprone and not necessarily at the end of the study period.

**Table 2. Definition of Successful Chelation Therapy**

Primary endpoint	
• Based on Serum Ferritin	
Serum Ferritin at Baseline	Success
>2500 µg/L	A ≥20% decline in serum ferritin from baseline within 1 year of Ferriprox therapy.
Secondary endpoints	
• Based on Liver Iron Concentration (LIC)	
LIC at baseline	Success
≥ <sup>(b)</sup> <sub>(4)</sub> mg Fe/g dw	A ≥20% decline in LIC from baseline within 1 year of Ferriprox therapy
• Based on Cardiac Iron Concentration (as assessed by MRI T2*)	
MRI T2* at baseline	Success
<20 ms	A ≥20% increase in MRI T2* from baseline within 1 year of Ferriprox therapy

dw = dry weight; LIC = liver iron concentration

a The proposed 20% reduction in SF or MRI T2\* is based on the 17% reduction in LIC from baseline (from 14.1 to 11.7 mg Fe/g dw) observed during therapy with deferasirox in the pivotal study 0107. (NDA 21-882, Exjade (deferasirox, ICL-670))

### Statistical Analysis Plan

Data will be derived from the integrated data provided in the Integrated Summary of Efficacy in the NDA. Additional data will come from Studies LA30-0307, LA28-CMP and LA04/06B updated to May 11, 2010. Data management processes for data entry, discrepancy management, quality control and reporting will remain standard as per each specific study protocol and clinical study report. Case report forms will not be created for the purposes of the study (CRFs were collected and processed as per each clinical study protocol).

Demographic characteristics, primary disease, and previous chelation therapy received will be summarized using descriptive statistics.

If there is more than one baseline measurement of a variable, the mean value for that variable will be used as the baseline value. For two of the studies (LA-03,

Borgna-Pignatti), the baseline serum ferritins are on the date of the first use of deferiprone or from the year before the first use of deferiprone.

The primary efficacy endpoint is the change in serum ferritin concentration, and the secondary endpoints are the changes in cardiac MRI T2\* and LIC. A binary endpoint of “success” or “failure” for each primary and secondary endpoint will be calculated based on the criteria shown in Table 2. The success rate will be determined for each efficacy variable and a 95% confidence interval of the observed success rate will be calculated based on a normal approximation. If the lower limit of the CI for any efficacy measure is greater than the pre-defined criterion of treatment success (20%), the therapy will be considered to be a success for that particular variable.

### **III. Conclusions**

In this submission, the sponsor has responded to a recommendation from the Division that, although deferiprone was not approved for the original indication proposed by the sponsor, there might be a reconsideration of the drug if the indication proposed would be more in line with the indication for deferiprone in most of the countries in which it is currently marketed, to wit, “for the treatment of transfusional iron overload in patients with thalassemia major when deferoxamine therapy is contra-indicated or inadequate”.

The sponsor intends to review already available data on serum ferritin, cardiac MRI T2\* and LIC as measures of body iron burden before and after 1 year of treatment with deferiprone in patients who could not be adequately treated with other approved chelator therapy (this would be mostly for patients treated with deferoxamine and a small number of patients treated with deferasirox). The source of the data will be the studies previously submitted in the NDA with the addition of data from completed studies of a liquid formulation of deferiprone and a continuing compassionate use program.

There are a number of concerns raised by the sponsor’s proposed study as the basis for determining the efficacy and safety of the use of deferiprone for the proposed indication:

- Patient population
  - The title of the protocol suggests that the indication may apply to all patients with transfusional iron overload. Virtually all the patients studied in the sponsor’s studies had thalassemia as the cause of anemia for which transfusions were required. Unless there are data supplied for patients with other causes of chronic anemia and the need for transfusion therapy (sickle cell disease,

myelodysplastic syndrome, aplastic and other anemia), the indication should be restricted to patients with thalassemia.

- Endpoints
  - In regard to serum ferritin, while it is believed that levels in excess of 2500 µg/L are associated with a worse outcome in patients with thalassemia compared to in patients with a level less than 2500 µg/L, there are no data that a 20% decrease in serum ferritin confers any clinical benefit for a patient (for example, decreasing the serum ferritin from 5000 µg/L to 4000 µg/L). Yet this change would be considered a success for a patient treated with deferiprone.
  - In regard to LIC, the sponsor's use of the results of Deferasirox Study 0107 (see footnote in Table 2 above) as a comparator does not take into account the fact that persons in Study 0107 were initially dosed based on baseline LIC, some done by SQUID which is known to underestimate the LIC, and were therefore given a dose that was less than what is now known to be therapeutic. Additionally, as with other chelators, those with higher body iron burdens tend to be more responsive to chelator therapy compared to those with a lesser body iron burden. Currently, it is believed that patients with LIC < 7 mg Fe/g dw are not generally subject to the adverse effects of iron toxicity in most body organs. The clinical significance of a decrease of ≥ 20% in LIC is not known.
  - In regard to cardiac MRI T2\*, as was the problem with the data provided in the Study LA16-0102, I am not aware of any data that show that an increase in T2\* of 20% or greater in a patient with a baseline T2\* of < 20 ms has any clinically meaningful significance.
  - The sponsor will claim success for any patient whose defined improvement occurs in ANY of these variables, rather than in ALL of the variables (for example, a fall in serum ferritin would be a success even if the LIC were rising and the T2\* were falling in the same patient). Such inconsistencies among the findings for the efficacy parameters among and within patients would weaken the persuasiveness of the results.
- Definition of failure of other chelating agents
  - The protocol does not state the length of treatment time nor the rate of fall in serum ferritin (or LIC or T2\* for that matter) that the person must have experienced while receiving other chelation therapy before being considered a failure on that therapy. For instance, if the patient had been receiving other chelation therapy for 9 months and the serum ferritin had fallen from 9000 µg/L to 3000 µg/L, that person could be considered to be a failure and would be eligible to be enrolled in the study even though there had clearly been some response to therapy.

- The dose of deferoxamine that the patient may have been receiving (20-40 mg/kg/d) when declared to be a failure appears to be too low to make that declaration. Although the label for deferoxamine states that the dose is 20-40 mg/kg/d, in practice the dose administered often is increased to up to 50 mg/kg/d if adverse reactions are not encountered.
- Study design and validity of data
  - This is a retrospective analysis of data already accumulated. There must be rigid rules in the protocol that spell out the exact methods for eliminating bias in the study.
  - To help ensure objectivity and minimize bias, there will need to be a separate group to review the data for eligibility to enroll in the trial and another group to analyze the data for efficacy and safety. Data cannot be shared between the two groups.
  - For many of the studies referenced to be included in the study, there did not seem to be patients who were commenced on deferiprone because of failure while receiving another chelation agent. The sponsor must use the utmost care in adhering to the inclusion/exclusion criteria established for the study.

#### **IV. Recommendations**

The sponsor's proposal has a number of shortcomings (as expressed above) that will limit the ability of the proposed study to support the efficacy and safety of the use of deferiprone in patients with transfusional hemosiderosis, even for the restricted indication.

The comments made in the conclusions above should be forwarded/conveyed to the sponsor.

The protocol should be reviewed by Statistics and any comments made by them should be incorporated into the response forwarded to the sponsor.

The sponsor should be asked to submit the final protocol to the IND (45724) for review before commencing the study.

**Appendix 1. Table of all studies from which patient data will be extracted and analyzed.**

**Table 1. Listing of Studies Used to Gather Data to Evaluate the Efficacy of Deferiprone in Patients with Iron Overload for Whom Previous Chelation Therapy Has Been Inadequate.**

Number	Title	Location	Number of Subjects: Entered/Completed	Study Type	Primary Objective	Available Efficacy Measurements for Analysis*		
						Serum Ferritin	LIC	MRIT2*
LA-01	Randomized Trial of L1 and Deferoxamine in Thalassemia Major	Canada	DFP: 35/27 DFO: 36/30	Randomized, open-label, active-controlled	To compare the relative effectiveness and safety of DFP and DFO therapy, as reflected by the ability of each chelator to achieve net negative iron balance, reduce tissue iron stores, and reduce body iron stores	√	√	
LA-02/06	Trial of APO-66 (Deferiprone) in Thalassemia/Maintenance Study Protocol of Deferrum™ (Ferriprox) for Subjects with Thalassemia who Complete Apotex Protocol LA-02	United States, Italy	DFP: 187/70	Open-label, uncontrolled	To monitor long-term safety and effectiveness of a fixed dose of deferiprone	√		
LA-03	The Long Term Efficacy and Safety of Deferiprone in Subjects with Thalassemia	Canada	DFP: 29/25	Open-label, uncontrolled, compassionate use	To assess the long-term efficacy and safety of DFP in patients with thalassemia and iron overload	√	√	
LA-04/06B	Compassionate-use of Deferiprone (L1) in Subjects with Iron Overload	Canada, Italy, United States		Open-label, uncontrolled, compassionate use	To provide patients with thalassemia or other chronic iron overload conditions unable or unwilling to take DFO with an alternative treatment to control iron overload	√	√	√
LA08-9701	Safety and Efficacy of Alternating Deferoxamine and Deferiprone compared with Deferoxamine Alone in the Treatment of Iron Overload in Thalassemia Subjects	Italy, Greece	Alternating DFP and DFO: 29/29 DFO: 30/30	Randomized, open-label, parallel, active-controlled	To evaluate efficacy and safety of alternating use of DFP and DFO compared with current standard therapy with DFO in treatment of iron overload	√	√	

Number	Title	Location	Number of Subjects: Entered/Completed	Study Type	Primary Objective	Available Efficacy Measurements for Analysis*		
						Serum Ferritin	LIC	MRIT2*
LA-11	Efficacy and Safety of Deferiprone (L1) in β-Thalassemia/Hemoglobin E Diseases Subjects in Thailand	Thailand	DFP: 24/16	Open label, uncontrolled	To study the efficacy and toxicity of DFP in patients β-thalassemia/Hb E diseases in Thailand	√		
LA-12-9907	Retrospective Assessment of Heart Failure and Survival During Iron Chelation with Deferiprone or deferoxamine in Subjects with Transfusion-Dependent β-Thalassemia	Italy	DFP: 54 DFO: 75  The study assessed existing data so study completion or withdrawal was not defined.	Open-label, parallel, longitudinal, active-controlled	To evaluate incidence of cardiac disease and survival in subjects treated with DFP compared with DFO over the same time period	√	√	
LA15-0002	Safety and Efficacy of Ferriprox™ for the Treatment of Iron Overload in Subjects with Transfusion-dependent Thalassemia in Iran	Iran	DFP: 29/26	Open label, uncontrolled	To monitor the efficacy and safety of DFP for the treatment of iron overload in subjects with transfusion-dependent thalassemia, as reflected by: serum ferritin concentrations the occurrence of AEs	√		
LA16-0102	Randomized Trial Comparing the Relative Efficacy of Deferiprone to that of Deferoxamine in Removing Excess Cardiac Iron in Thalassemia Major Subjects	Greece, Italy	DFP: 29/27 DFO: 32/29	Randomized, open-label, active controlled	To determine whether orally administered Ferriprox® (deferiprone) exhibits superior efficacy in removing excess iron from the heart compared to that of standard subcutaneous infusions of Desferal® (deferoxamine), as reflected by Magnetic Resonance Imaging T2-star (MRI T2*) assessments of the heart in subjects treated with either chelator	√	√	√
Borgna-Pignatti et al. (2006) <sup>40</sup>	Cardiac Morbidity and Mortality in Deferoxamine- or Deferiprone-treated Patients with Thalassemia Major	Italy	DFP: 157 DFO: 359	Retrospective, natural history	To compare the occurrence of cardiac disease in patients treated only with DFO to those whose therapy was switched to DFP during the period of observation, from 31 JAN 1995 to 31 DEC 2003	√		

Number	Title	Location	Number of Subjects: Entered/Completed	Study Type	Primary Objective	Available Efficacy Measurements for Analysis*		
						Serum Ferritin	LIC	MRIT2*
LA28-CMP	The compassionate use/named patient program of Ferriprox oral solution in iron-overloaded pediatric patients with transfusion-dependent anemias	Egypt, Malaysia, Singapore	DFP: 83/62	Multi-center, open label, single treatment, uncontrolled, compassionate use/named patient basis program	To provide treatment with Ferriprox oral solution to iron-overloaded pediatric patients with transfusion-dependent anemias for whom deferoxamine is contraindicated or inadequate.	√		
LA-30	24-week open label, uncontrolled study of the safety and efficacy of Ferriprox (deferiprone) oral solution in iron-overloaded pediatric patients with transfusion-dependent anemia	Egypt, Indonesia, Malaysia	DFP: 100/95	Open label, uncontrolled	To assess the safety of Ferriprox oral solution for the treatment of iron overload in pediatric patients with transfusion-dependent anemia.	√		

AE = adverse event; MRI T2\* = magnetic resonance imaging T2\*; DFO = deferoxamine; DFP = deferiprone; LIC = liver iron concentration.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	ORIG-1	AOPHARMA INC	FERRIPROX (DEFERIPRONE)

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/s/

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GEORGE G SHASHATY  
07/12/2010

KATHY M ROBIE SUH  
07/12/2010

MEMORANDUM      DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

Date:            December 31, 2009

From:            Kathy M. Robie-Suh, M.D., Ph.D.  
Medical Team Leader, Hematology  
Division of Medical Imaging and Hematology Drug Products (HFD-160)  
Office of Oncology Drug Products

Subject:         CORRECTION ADDENDUM to Medical Team Leader (CDTL) Review  
Ferroprox (deferiprone), submitted 1/29/09 (final reviewable unit); review  
completed 11/20/09 (signed 11/25/09)

To:                NDA 21-825

This Addendum is to correct a typographical error in my Medical Team Leader (CDTL) Review of NDA 21-825 completed November 20, 2009 (signed in DARRTS November 25, 2009).

On page 4, second line of text, the parenthetical expression should be '(34% vs. 14%)' such that the sentence reads:

“Baseline characteristics were comparable between the two treatment groups, except that somewhat more patients in the deferoxamine group were splenectomized as compared to in the deferiprone group (34% vs. 14%).”

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-21825	----- ORIG-1	----- AOPHARMA INC	----- FERRIPROX (DEFERIPRONE)

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/s/  
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KATHY M ROBIE SUH  
12/31/2009

MEMORANDUM      DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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Date:            November 20, 2009

From:            Kathy M. Robie-Suh, M.D., Ph.D.  
Medical Team Leader, Hematology  
Division of Medical Imaging and Hematology Drug Products (HFD-160)  
Office of Oncology Drug Products

Subject:         Medical Team Leader (CDTL) Review  
Ferriprox (deferiprone), submitted 1/29/09 (final reviewable unit)

To:                NDA 21-825

Ferriprox (deferiprone) is an orally active iron chelator being developed for use in treating iron overload. In this application the sponsor is seeking marketing approval of Ferriprox for:

- Treatment of iron overload in patients with transfusion-dependent thalassemia
- Treatment of iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate

The proposed dose is Ferriprox is 25 to 33 mg/kg body weight, orally, three times a day for a total daily dose of 75 to (b) (4) mg/kg body weight.

**Background:**

Patients with certain inherited anemias (importantly  $\beta$ -thalassemia and increasingly sickle cell disease in the U.S.) require frequent transfusion of red blood cells beginning at a young age to offset anemia due to anemia secondary to inability to manufacture normal hemoglobin. Normally, there is a regulated absorption of iron from the diet of about 1 mg daily which maintains a total body iron of approximately 3 to 5 grams in adults (about 50 mg/kg in men and 35 mg/kg in menstruating women). Each transfused unit of packed red blood cells contains about 200 mg of iron. Because the body has no physiologic mechanism to excrete excess iron, repeated red blood cell transfusions over time result in massive iron overload. The excess iron becomes deposited in tissues and causes tissue damage due to iron-catalyzed peroxidation of membrane lipids and leads to morbidity and often eventually mortality, mainly due to cardiac damage. The liver and endocrine organs also are notably affected. Assessment of liver iron content (LIC) by liver biopsy is the generally accepted standard for assessment of body iron burden.

Currently available treatment options for management of iron overload due to transfusions include Desferal (deferioxamine mesylate), an injectable iron chelator approved in 1968 and Exjade (deferasirox), an orally active iron chelator approved in 2005.

Deferiprone, first used in humans in 1987, has been under development for a number of years. It was approved in the European Union in 1999 and is approved in a number of countries worldwide. The IND for deferiprone (IND 45724) was opened 7/15/94. Orphan Drug designation was granted on 12/12/01 and Fast track designation was granted 1/26/04. The fact that the drug was granted Fast Track designation reflects the serious nature of the condition for which the drug is intended to be used and the fact that at the time the designation was granted the only therapeutic option for these patients was deferioxamine which must be administered via continuous subcutaneous infusion over many hours each day and which, therefore, is difficult for many patients to comply with and/or tolerate. Pre-NDA meetings were held with the sponsor on 7/9/04 and another on 5/15/06. The NDA submission was accepted for submission under the Continuous Marketing Application (CMA)-Pilot 1 program (“rolling review”) and the first reviewable unit (Pharmacology and Toxicology information) was submitted on 12/21/06 (received 12/22/06). The final reviewable unit (Clinical and Statistical) was submitted on 1/29/09 (received 1/30/09).

A major issue with this application is the use of a new methodology to evaluate extent of iron overload and effectiveness of chelation therapy. This involves use of magnetic resonance imaging of the heart (cardiac MRI) with measurement of a parameter termed T2\* (T2 star). Approvals of Desferal and Exjade were based on measurement of liver iron concentration by biopsy (LIC). Internal consultation with CDER imaging experts in the Division of Medical Imaging and Hematology (DMIHP) regarding status of cardiac MRI T2\* assessment as a measure of cardiac iron content and clinical significance of small changes in MRI T2\* with chelation therapy concluded that “cardiac T2\* MRI technology is not validated as a quantitative measure of cardiac iron content in humans” and “the clinical significance of a small change in T2\* has not been shown.” (Medical Officer’s Consultative Review Memorandum by Dr. M. Fedowitz, completed 4/15/09 (signed 4/28/09)). The review cited a number of potential sources of variability that might affect T2\* measurements including artifacts from non iron variables (lungs, tissue oxygenation, blood flow, body size, cardiac motion), quality control of image acquisition and variability from site to site, reader’s interpretation, few human studies comparing cardiac T2\* measurements with tissue iron concentration and little information on the relationship between T2\* and cardiac function and on the sensitivity of the measurement to treatment response. The review did find that “There is an inverse relationship between cardiac T2\* and cardiac iron content, however the correlation is not high.” Review of the use of cardiac MRI by S. S. Rajan, Ph.D., Office of Device Evaluation, Center for Devices and Radiological Health (CDRH) concluded based on a literature publication (Anderson et al. Eur Heart J. 2001. 22: 2171-79 ) that “In all likelihood the changes in the T2\* values in myocardial tissue is a consequence of changes in iron content, even

though it could have been caused by changes in other paramagnetic species or unrelated local magnetic field inhomogeneities. The high iron concentrations provides a dominant mechanism for the short T2\* values.” The review also found based on the paper that the myocardial iron content [based on T2\*] cannot be predicted from serum ferritin or liver iron. The review commented based on the publication that even though the authors do not have biopsy correlation of iron levels with T2\*, the data supported a correlation of ventricular dysfunction with T2\* values. Regarding the relationship between change in T2\* and change in cardiac status, the CDRH review concluded based on literature review that “...a change from 13 to 17 ms in the value of T2\* is a significant change in status.”

### **Findings of Clinical Review:**

The primary clinical review of deferiprone was conducted by Dr. G. Shashaty (signed 10/19/09). To support the effectiveness of deferiprone for the indication the sponsor has submitted one pivotal open-label, comparative efficacy and safety study (Study LA 16 0102), which was a study in adult  $\beta$ -thalassemia patients with transfusional hemosiderosis, and a main supporting retrospective, single center study of heart failure and survival during iron chelation with deferiprone or deferoxamine in patients with transfusion-dependent  $\beta$ -thalassemia. Neither study was conducted under IND or had protocol review by FDA. Additional use data are provided from some studies of longer-term use of deferiprone and use of deferiprone in conjunction with deferoxamine.

#### Efficacy:

##### ➤ Pivotal Study: Study LA 16 0102:

Study LA 16 0102 was a multicenter (4 hospitals in Greece and Italy), randomized, open-label, active controlled clinical trial comparing the use of deferiprone versus the use of deferoxamine in removing excess cardiac iron in subjects with thalassemia major. The primary objective of this study was to determine whether orally administered deferiprone exhibits superior efficacy in removing excess iron from the heart compared to that of standard subcutaneous infusions of deferoxamine, as reflected by MRI T2\* assessments of the heart in subjects treated with either chelator. Patients were randomized to treatment with deferiprone 100 mg/kg/day in 3 divided doses (initiated at 75 mg/kg/day and increased over 7 weeks to final dose) or deferoxamine 50 mg/kg/day by subcutaneous infusion 5 to 7 days a week. Subjects were consenting adult patients with transfusion-dependent thalassemia major receiving deferoxamine for at least the prior 5 years and not receiving deferiprone for at least the prior 2 years having a T2\*  $\geq 8$  ms and  $< 20$  ms at study entry. Patients were stratified into two groups based on baseline T2\* (8 to  $< 14$  ms and 14 to 20 ms). The study enrolled and treated 61 patients (32 with T2\* in the lower range and 29 with T2\* in the higher range). A total of 29 patients were randomized to deferiprone and 32 to deferoxamine. About 51% of patients were male, mean age was 25.6 years and all patients were Caucasians. Half of the patients were hepatitis C positive and one quarter had undergone splenectomy. Twenty-nine (29) patients were randomized to deferiprone and 32 to deferoxamine. Baseline characteristics were comparable between the two treatment groups, except that somewhat

more patients in the deferoxamine group were splenectomized as compared to in the deferiprone group (345 vs. 4%). The sponsor's primary efficacy analysis presented in the study report used log transformed data and is shown below:

**Table 7.4.1.1-1 Log (MRI T2\*) between Ferriprox and Desferal Treatment Groups - ITT Population**

MRI T2* (milliseconds)	Randomized Treatment Groups					
	Baseline		6 Months		12 Months	
	Ferriprox [n=29]	Desferal [n=32]	Ferriprox [n=29]	Desferal [n=31] <sup>†</sup>	Ferriprox [n=29]	Desferal [n=31] <sup>†</sup>
Geometric Mean (milliseconds) <sup>*</sup>	13.03	13.32	15.37	14.43	16.51	15.01
Coefficient of Variation (%) <sup>‡</sup>	32	30	38	37	38	39
Percentage of Baseline			118	109	127	113
Ratio of Means (%) <sup>§</sup>	98		109		112	
p-value <sup>  </sup>	0.7731		0.0404		0.0228	

Source: [Appendix 12.1.9 \(Statistical Report, Appendix 2.1.1\)](#)

\* Geometric mean is defined as antilog of the mean of the log data

† Subject C1-40 had baseline MRI T2\* level value only and was not eligible to be included in the ITT population.

‡ Coefficient of variation is defined as  $\sqrt{[e^{\text{variance}} - 1]}$ , where variance is the variance of the mean in log scale.

§ The ratio is defined as Ferriprox mean/Desferal mean. At 6 and 12 months, the ratio is corrected for the difference in baseline mean between the two treatment groups by dividing it by 0.98.

|| The Log (MRI T2\*) between the Ferriprox and Desferal treatment groups was compared by the two-sample t-test.

The sponsor claimed a statistically significant difference between treatment groups in mean change in T2\* from baseline to 12 months (p=0.0228). The protocol specified primary analysis using the untransformed data for the ITT analysis found a change from baseline to 12 mos of 3.9 ms for the deferiprone group (N=29) and 2.3 ms for the deferoxamine group (N=31) with a non-significant p-value of 0.0993 (t-test) for the between group comparison (Statistical Review, S. Misra, Ph.D., 11/10/09). However, FDA statistical review found that assumption of normal distribution for t-test was not met for the non-transformed or for the log transformed data and therefore use of non-parametric analyses was the appropriate analysis. Post-hoc statistical analysis by FDA using non-parametric methods showed a median change in the difference from baseline at 12 months for MRI T2\* of 1.0 in the Deferoxamine group as compared to 3.7 in the Deferiprone group. This difference was statistically significant (p=0.0048 (Median Test)). Similarly, the distributions of the change in the difference from baseline at 12 months for MRI T2\* were found to be statistically significantly different (p=0.0168 (Kolmogrov-Smirnov Test) in favor of deferiprone.

Analyses of secondary endpoints showed: a trend in favor of deferiprone in terms of MRI T2\* at 6 months, greater increase with deferiprone in left ventricular ejection fraction (LVEF) by cardiovascular magnetic resonance (CMR) and echocardiogram (ECHO), no differences in changes in LIC between treatments. The review noted that these analyses also were limited by the same normality issues as for the primary efficacy analysis. Mean LVEF in the deferiprone group at baseline was 69.7% by CMR and 64.7% by ECHO and increased by 3.1% (CMR) and 2.5% (ECHO) at 12 months. In the deferoxamine group, mean LVEF at baseline was 68.4% by CMR and 64.3% by ECHO and increased by 0.3% (CMR) and decreased by 0.6% (ECHO) at 12 months. Evaluation of the relationship between LVEF and MRI-T2\* was done by FDA Statistics and showed: “There were no statistically significant correlations between the MRI T2\* and the ECHO LVEF or the ECHO LVSF at baseline or at any follow-up evaluation, nor with the change in ECHO LVEF or the ECHO LVSF at the end of the study. There were modest correlations at 6 (nominal p values= 0.027) and 12 (nominal p values= 0.015) months of therapy between the MRI T2\* and the MRI LVEF but not at baseline (nominal p value, 0.2329). The maximum correlation was 0.31. These data suggest that, at best, the change in MRI T2\* explains approximately 10% of the variation in heart function as measured by MRI LVEF, ECHO LVEF or ECHO LVSF.” The clinical reviewer (Dr. G. Shashaty, signed 10/19/09) also considered literature information provided by the sponsor in support of use of CMR to evaluate cardiac function and utility of cardiac MR T2\* and made the following comments (*italics*):

- “*CMR appears to be able to provide an assessment of left ventricular volumes and ejection fractions, but its correlation with LVEF obtained by echocardiography is imperfect because the latter method has a lower accuracy.*”
- *The reference provided for the sponsor’s assertion in Bullet #2, above, (Oliveri NF et al NEJM 1994; 331:574-578) was a study of the effects of deferoxamine therapy on morbidity and mortality in patients with thalassemia. The article indicates that patients with thalassemia have better outcomes when their serum ferritin is consistently <2500 µg/L compared to serum levels consistently in excess of that number. Nowhere in the article can I find any data on “the linking of ventricular function and myocardial T2\*”. In addition, I believe that the article was published prior to any significant studies that measured T2\*, all of which commenced in the 21st century.*
- *CMR T2\* values below 10 ms appear to be associated with a greater frequency of the development of cardiac failure within one year compared to patients with CMR T2\* values above 10 ms.*
- *It appears that liver T2\* measurements have a curvi-linear inverse relationship with LIC as obtained by biopsy.*

*In clinical practice, measurements of serum ferritin and LIC have been the generally accepted methods of evaluation of the efficacy of therapy in persons with iron overload.*

*Acceptance of the sponsor's method of measuring the endpoint is dependent upon several assumptions, some of may not be true.*

- *First, I accept that excess iron in the heart is detrimental to cardiac function.*
- *Second, I have some reservations of the ability of the MRI T2\* to accurately measure true iron concentration. The data presented by Dr. Pennell were performed in "ex vivo" hearts, rather than on MRI T2\* performed during life shortly before death and then spectrometrically measured for iron content after death. Importantly, the data presented by Dr. Pennell contain no information on the iron content of hearts with MRI T2\* measurements between 13.96 and 33.56 ms, and it is within these bounds that most persons with transfusion dependent thalassemia reside.*
- *Although it seems logical to conclude that an increase in MRI T2\* of the heart should be associated with improvement in function of the heart that would benefit both morbidity and mortality outcomes, there are no scientific data presented that support such a conclusion.*
- *The sponsor has not submitted any data as to the quantitative increase in the MRI T2\* that is required to indicate a clinical benefit in mortality or morbidity in iron overloaded thalassemia patients.*

*Therefore, I am not certain that I can accept MRI T2\* as even a surrogate endpoint."*

For Study LA 16 0102 the FDA Statistical Review concluded: "This single randomized trial LA16-0102 has serious limitations including imaging endpoint of MRI T2\*, no "within study" evidence that MRI T2\* is reasonably likely to predict meaningful clinical outcome, "primary" analysis questionable due to lack of normality, inadequate safety database of only 29 patients exposed to deferiprone, and the observational study LA 12-9907 not providing independent corroboration due to serious limitations including lack of randomization, no information regarding some important baseline variables such as splenectomy status, and limited information (a lot of missing values) at baseline such as hepatic iron concentration. The submitted data does not support the proposed indications."

The Clinical Review stated a number of deficiencies in the study including: inadequacy as a single study to support efficacy [small sample size, limited number of institutions (3), no evidence of decrease in serum ferritin or LIC (which are most often accepted as evidence of efficacy for the use), and lack of sufficiently robust statistical result], use of a surrogate efficacy endpoint (MRI T2\*) that has not been previously used as an efficacy endpoint for a phase 3 study to support NDA approval and lack of evidence of a relationship between change in MRI T2\* and clinical benefit on mortality or morbidity in patients with transfusion-dependent hemosiderosis, uncertain clinical meaningfulness of observed small increases in LVEF and LVSF, exclusion of more than half of patients in the target thalassemia population (based on screening data from the study) due to insufficiently low baseline MRI T2\* and exclusion of pediatric patients (who comprise a significant proportion of the thalassemia population). A Consultation Review from the Division of Cardiovascular and Renal Drug Products (DCRDP) obtained to seek

comment on the LVEF and LVSF findings in the clinical trials commented that these values could be influenced by loading conditions (such as decreased ejection fraction with hypertension which increases afterload and with hypovolemia which decreases preload). The review commented that, "Our Division has not accepted changes in ejection fraction or fractional shortening as surrogate endpoints in lieu of meaningful clinical benefits (e.g., improved survival, decrease in heart failure hospitalization, improved exercise capacity)." The review concluded, "Meaningful clinical outcomes (e.g., heart failure, heart failure hospitalizations, mortality) should be used as the basis for a claim for reducing heart failure incidence." The reviewer was not able to evaluate the clinical meaningfulness of small changes in ejection fraction or fractional shortening. (Dr. S. Targum, 4/20/09).

In conclusion, overall clinical review found inadequate evidence of efficacy to support a recommendation for approval of the application (Clinical Review by Dr. G. Shashaty, 10/19/09). Similarly, the overall recommendation on efficacy from FDA Statistical review was that the submitted data does not provide robust and meaningful statistical evidence to support the efficacy of deferiprone for the proposed indications (Statistical reviews by S. Misra, Ph.D., 11/10/09 and by J. Zalkikar, Ph.D., 11/22/09).

➤ Major Supportive Study: Study LA 12 9907:

This was a single center, retrospective observational analysis of medical records of transfusion-dependent  $\beta$ -thalassemia patients being followed in a transfusion program at a single institution in Italy. Dose was stated as 75 mg/kg/day but was adjusted to degree of iron overload resulting in doses from 35 to 100 mg/kg/day. Patients in this program were being followed with a prospective survey on complications and survival. Patients had periodic cardiac examination, including medical history, echocardiography, electrocardiogram and Holter monitoring, quarterly serum ferritin levels and transfusional iron input. Beginning in 1995 some patients received deferiprone for iron overload; others received deferoxamine. Data for the study were collected for patients from December 1995.

Of 129 patients included in the analysis, 75 had received deferiprone and 54 had received deferoxamine. About 47% were female; mean age was 18 years. Baseline characteristics were similar except that mean age at start of chelation was somewhat older and mean LIC (by SQUID) was less in the deferoxamine patients. (Many fewer deferoxamine than deferiprone patients had SQUID LIC determined and only deferiprone patients had biopsy LIC). The sponsor found a significant difference between therapy groups for the proportion of patients with worsening of NYHA classification from the first to the last assessment (deferoxamine, 20.6%; deferiprone, 4.3%;  $p=0.0069$ ), and with cardiac disease at the last assessment among patients who were initially cardiac disease-free (deferoxamine, 29.3%; deferiprone, 13.0%;  $p=0.0133$ ). There were 4 deaths during the study all among deferoxamine-treated patients, 3 attributed to cardiac disease [2 of these had NYHA Class II throughout observation, 1 started as Class I and deteriorated to Class

IV prior to death], 1 died in a motor vehicle accident (Clinical Review, Dr. G. Shashaty, 10/19/09). The Clinical Review also indicates that there were no significant differences in ejection fraction or shortening fraction from baseline to end of study for either treatment or between treatment groups nor were there differences between groups in frequency of arrhythmia. Patients in the deferiprone group were slightly more likely to be compliant and average drug exposure time was greater in the deferoxamine group (5.9 yrs) as compared to the deferiprone group (5.3 yrs).

Because of deficiencies in study design (retrospective, poorly defined cardiac endpoints, some differences in baseline characteristics) Study LA 12 9907 was not helpful to establish efficacy.

➤ Additional Randomized, Controlled Study: Study LA-01:

Prior to Study LA 16 0102, the sponsor had conducted another prospective, randomized, open-label, controlled clinical study of deferiprone compared to deferoxamine. However, this study was not included as a pivotal study due to problems with the conduct of the study as stated by the sponsor. Design and results of this study are summarized below.

LA-01 was a prospective, randomized, open-label, controlled clinical study of deferiprone (25 mg/kg tid) compared to deferoxamine (50 mg/kg/day, 4 to 7 times a week) for a treatment duration of 2 years conducted by the sponsor at two locations in Toronto, Canada and one in Montreal, Canada. At the conclusion of two years of treatment patients were followed for an additional year. The aim of the study was to compare efficacy of the two treatments at 24 months (primary efficacy variable) based on: change in liver iron concentration (LIC) assessed by superconducting-quantum-interference-device (SQUID)(preferred) or by liver biopsy. The sponsor expected that the two treatments would be “comparable” or “similar” in efficacy and toxicity. A sample size of 33 patients in each treatment group was estimated to be adequate to detect if the mean liver iron concentration of the deferoxamine groups is less than 80% of the expected value for deferiprone ( $\alpha=0.05$ ).

The study was conducted from October 1993 to August 1996. As explained by the sponsor in the submitted study report (revised version dated June 9, 2006) the Toronto sites (HSC and TGH) were terminated during the third year of the study “due to irreconcilable differences and ongoing problems with the principal investigator, which included the failure to meet the obligations outlined in the Drugs Directorates guidelines on ‘Conduct of Clinical Investigations’, and the sponsor’s concern regarding the safety of the patients.”

An interim analysis was conducted in January 1998 using all available data up to 8/31/96. At this time a total of 71 patients had been randomized and received study drug (35 deferiprone, 36 deferoxamine). Of these, 40 patients had completed 24 months of treatment, 6 patients had completed 12 months and 25 patients had completed less than 12 months. Interestingly, 7 patients had completed 36 months of deferiprone treatment

while no patients had completed 36 months of deferoxamine treatments. The patients had a mean age of 16.5 years (range, 6.9-33.2 yrs) and 50% were males. There were about equal numbers of Greek, Italian and “other” patients and slightly fewer Indian and Asian patients. A total of 40 patients (20 deferiprone, 20 deferoxamine) had data available for determination of liver iron concentration. Demographics were similar to the overall population. The summary of liver iron concentration measured by SQUID or biopsy at baseline and 24 months based on the sponsor’s tables from the 1998 interim analysis is shown below:

**LA-01: 1998 Interim Analysis: Summary of LIC (mg Fe/g dry weight) by SQUID (preferred) or Biopsy**

Therapy	Baseline		24 months	
	N	Fe (SD)	N	Fe (SD)
Deferiprone	20	9.48 (5.48)	10	10.02 (2.08)
Deferoxamine	20	8.04 (4.99)	11	8.27 (4.91)

SD= standard deviation

There was no difference in mean responses between the two therapies. Of 11 patients (7 deferiprone, 4 deferoxamine), who had discontinued therapy prematurely by this time, among deferiprone patients, 2 experienced agranulocytosis, 2 had history of neutropenia, 1 experienced right-sided heart failure, 1 had a psychiatric condition and 1 had a *S. aureus* infection. Discontinuations among the deferoxamine patients were due to non-compliance (2), lost to followup (1) and patient request (1). All discontinuations were at the Toronto sites. Safety data were not summarized in the interim analysis.

The sponsor’s table below shows the site distribution of patients enrolled in the study at completion of the study (8/31/96 cutoff date).

**Table 3: Distribution of Patients by Site**

	HSC	MCH	TGH	Total
Deferiprone	28	4	3	35
Deferoxamine	23	3	10	36
<b>Total</b>	51 (71.8%)	7 (9.9%)	13 (18.3%)	71

Note: HSC=Hospital for Sick Children; MCH=Montreal Children’s Hospital; TGH=Toronto General Hospital.

Based on the patient listings 90% of enrolled patients were at the Toronto sites. The duration of treatment for patients at the Toronto sites ranged from 9 to 32 months. Of 71 enrolled patients who received study drug, 35 were randomized to deferiprone and 36 to deferoxamine. The patients had a mean age of 16.0 years (range, 6.0-33.0 yrs) and 50% were males. About 50% were white and 50% were non-white. Of these, 21 in each treatment group completed the study. At the end of the study a total of 16 patients (9 deferiprone, 7 deferoxamine) had withdrawn prior to completing 24 months of therapy.

In addition to the 11 mentioned above for the interim analysis, these included 2 deferiprone patients (1 who experienced an apparent doubling of liver iron on biopsy over first 18 months and 1 who was withdrawn due to study terminated by sponsor) and 3 deferoxamine patients (2 due to refused liver biopsy and 1 due to study terminated by sponsor).

Efficacy results at end of study are shown in the sponsor's table below:

**Table 4: Mean Liver Iron Concentration at Baseline and Month 24 (mg/g dry weight)**

Therapy	Baseline	Month 24	Change from Baseline	P-value
Deferiprone (N=13)	8.54 ± 3.64	8.90 ± 2.83	0.36 ± 4.87	0.7962
Deferoxamine (N=13)	7.09 ± 4.06	7.78 ± 4.68	0.69 ± 3.40	0.4798

Among 13 patients in each treatment group who completed 24 months of treatment and had both baseline and 24 months LIC data available, there were no significant differences between the groups in the baseline, 24 months, or change in LIC. The sponsor interpreted the results of this study as indicating that deferiprone is as effective as deferoxamine in controlling body iron load in transfusion-dependent patients.

The sponsor's 6/9/06 study report for LA-01 indicates that as of the cutoff date of 8/31/96, duration of deferiprone therapy ranged from 0.22 years to 2.77 years, with a mean of 1.64 years and duration of deferoxamine therapy ranged from 0.66 years to 2.67 years, with a mean of 1.83 years. [Note: This seems inconsistent with the mention in the interim report that 7 patients had completed 36 months of deferiprone therapy. It should be noted that a notation at the bottom of table APPENDIX 15.2.1 showing study discontinuations for the interim analysis indicates a data cut-off date of 8/31/97]. Serious adverse events of agranulocytosis led to treatment withdrawal of 2 patients in the deferiprone arm. These patients recovered after hospitalization and treatment with G-CSF. Two patients mentioned above were discontinued from deferiprone because of history of "cyclic neutropenia". (Other patients had single low neutrophil counts and were continued in the study without event). The sponsor considered the patient who experienced right heart failure and discontinued deferiprone a "voluntary withdrawal". This patient subsequently died after heart transplant surgery (death considered unrelated). One patient on deferoxamine experienced symptomatic congestive heart failure and was not able to continue on study drug.

Thirty-five percent (35%) of patients in the study were hepatitis C positive at study entry. In deferoxamine-treated patients the incidence of ALT elevations >2 times upper limit of normal decreased over time in the study regardless of hepatitis C status. However, among deferiprone-treated patients those who were hepatitis C positive and receiving

deferiprone tended to have an increase in ALT elevations >2 times upper limit of normal with longer times in the study. These patients had significantly higher rate of ALT elevations >2 times upper limit of normal as compared to those receiving deferoxamine (p=0.0157). Among patients who were hepatitis C negative at baseline and were on deferiprone, the percentage of patients with ALT greater than twice the upper limit decreased significantly over time (p=0.0029).

Average neutrophil count (ANC) trends were examined, and a trend toward higher ANC with time was seen in the deferiprone-treated patients, however, values for patients who experienced agranulocytosis were excluded from the analyses.

*Reviewer's comments: Even if the issues of data completeness and validity are disregarded, this study is not very informative from an efficacy viewpoint and raises some safety concerns. The study does not demonstrate superior efficacy of deferiprone over deferoxamine (despite apparent greater compliance in the deferiprone treatment arm) for the defined efficacy endpoint of change in liver iron concentration measured by SQUID or biopsy. Though the sponsor claims the study shows that deferiprone is as effective as deferoxamine, the study is not designed or sized for and the statistical analysis plan does not specify a plan for non-inferiority analysis of the study results. Notable in the study is the occurrence of serious adverse events of agranulocytosis and a death due to heart failure among the deferiprone-treated patients. Also, notable is the observation that AST elevations >2 times upper limit of normal become more frequent with long treatment duration among patients with hepatitis C who are receiving deferiprone. The clinical significance of this observation is not unknown. The Clinical Reviewer commented that, "Flaws in the conduct of the study, completeness of data collection and analyses of the data preclude drawing any meaningful conclusions from this study."*

Safety:

The safety information in the application is reviewed, summarized and discussed in detail in the Medical Officer's review by Dr. G. Shashaty (signed 10/19/09). Only the major findings will be summarized here.

Estimated total exposure to deferiprone including post-marketing is 16,000 patient-years. In controlled clinical studies 118 patients received deferiprone (additional 29 received both deferiprone and deferoxamine). Most patients in clinical studies (88%) had thalassemia. From the Medical Officer's review, the significant safety concerns associated with deferiprone included most notably:

- Agranulocytosis -- occurred in about 1% of patients receiving deferiprone; development is unpredictable; may follow occurrence of neutropenia in some patients; does not appear to be dose related; improves upon discontinuation of the drug, however, deaths from sepsis have been reported during the period of agranulocytosis.
- Hepatic toxicity -- suggested because of an increase in transaminase levels in persons receiving deferiprone that improved following discontinuation of the drug

and an occasional patient who had an increase in transaminase levels upon rechallenge. One investigator reported increased fibrosis in the liver after several years of treatment with deferiprone. The clinical significance of these laboratory changes is clouded because persons with iron induced hepatic toxicity often exhibit waxing and waning of transaminase levels, iron deposition may lead to hepatic injury, and patients often develop infectious hepatitis because of multiple transfusions.

- Gastrointestinal adverse reactions -- include upper and lower gastrointestinal symptoms; pancreatitis
- Arthropathy – does not appear to be immune mediated; appears to resolve with the discontinuation of deferiprone.
- Cardiac --torsades-de-pointes has been reported in one patient.
- Neurological --. A cerebellar syndrome has been reported in several individuals who mistakenly received excessive doses of deferiprone over long periods of time. It is possible that this type of reaction is due to the use of deferiprone in persons whose iron overload has been relieved. Such reactions have been reported in non-iron overloaded patients being treated with deferiprone for the treatment of Freidrich's ataxia.
- Miscellaneous – reports of auditory, platelet, immunological and dermatological adverse reactions

The sponsor proposed a Risk Evaluation and Mitigation Strategy (REMS), particularly for monitoring for agranulocytosis.

*Special Populations:*

Deferiprone has been granted orphan designation; however, pediatric patients with  $\beta$ -thalassemia are likely to receive the drug if approved; hence, adequate investigation in pediatric patients is needed. Some pediatric patients were exposed to deferiprone during drug development, but none were included in the single pivotal controlled clinical study.

Comment on the pediatric information was provided by the Pediatric and Maternal Health Staff (PMHS)(Dr. A. Karesh (9/17/09). The clinical study database contained data on 111 pediatric patients (35 patients 6-11 years old, and 76 patients 12-15 years old) who received deferiprone at a dose of 75mg/kg/day. None were in the one pivotal study. Additional pediatric exposure is identified in the periodic safety update and the postmarketing exposure in 118 patients who received one or more deferiprone doses. The PMHS review found that there was inadequate analysis of the safety data by age and growth and developmental information was lacking.

Review of the application by the Maternal Health Team (MHT) recommended Pregnancy Category C labeling based on finding of severe adverse developmental effects in two species and recommended patient counseling on effective contraception (no contraindication recommended) (Dr. L. Sahin, 9/24/09).

**Other Information:**

Chemistry: Chemistry, manufacturing, and controls (CMC) information for the deferiprone NDA was initially submitted on 3/12/07 but was subsequently withdrawn. Since then there have been several submissions. The CMC information has been reviewed in detail by W. M Adams, Ph.D. (3/21/08; 10/20/09). Ferriprox (deferiprone) is produced as 500 mg oral, film-coated tablets in a 100-count bottle. The drug, deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one), is a bidentate iron chelator that preferentially binds ferric ions into a 3:1 (deferiprone: iron) complex at low pH. Deferiprone is highly soluble in water at pH 1-7.5 and has high permeability. Its molecular weight is 139.15 g/mol.

Review of the initial submissions identified deficiencies and an information request letter was issued on 2/29/08. Drug substance comments addressed the use of contract labs; the release specifications; the method validation studies; and the stability studies. The drug product comments addressed the use of contract labs; the excipient specifications; the release specification including the dissolution criterion; the method validation studies; certificates of analysis for packaging components and materials; and the stability studies. (Chemistry Review, W. M. Adams, 3/21/08)

CMC review (W. M. Adams, Ph.D., 10/20/09) states that there are several deficiencies that must be addressed before Ferriprox drug product can be approved. These include the following:

1. The regulatory methods have not been appropriately described and validated at each of the proposed drug substance and drug product manufacturing sites.
2. The storage condition statement for bulk drug substance should be revised to reflect the results of the stability studies.
3. The dissolution criterion should be revised to reflect the submitted drug release profile data.
4. Inadequate drug product stability data has been submitted to support the proposed expiry period.
5. CMC information in the proposed Patient Information Leaflet should be revised.
6. Type I DMF 10,867 for bulk drug substance has been reviewed and found deficient to support approval of the NDA. A deficiency letter has been issued to the holder.-

The review also notes that the overall EES recommendation for this application is Withhold dated 10/19/09.

Pharmacology: The pre-clinical pharmacology and toxicology information has been reviewed in detail by D. E. Bailey, Ph.D. (reviews signed 6/27/07, 8/4/08 and 9/22/09). Notable review findings from these reviews are summarized briefly here.

- The mechanism of action of deferiprone was characterized as “Deferiprone is a bidentate iron chelator that at physiological pH preferentially forms 1:3 iron:ligand complexes of Fe(III).”
- Deferiprone is absorbed readily from the gut and binds available iron from transferrin in the blood. The deferiprone iron complex is excreted primarily by the fecal route via the bile in rodents and marmoset but in monkeys and humans a greater amount is excreted in the urine.

- In a 12-month repeat dose toxicity study in rats there was a high incidence of metastatic malignant tumors of multiple organs (liver, lung, mammary gland, skin and thyroid) in males and females, independent of whether animals were naïve or iron-loaded. Tumor types observed included hepatocellular carcinoma, lung metastasis malignant histiocytoma, lung metastasis hepatocellular carcinoma, mammary adenocarcinoma, mammary carcinoma, mammary fibroadenoma, skin keratoacanthoma, skin malignant fibrous histiocytoma, skin fibrocyte fibroma and thyroid follicular cell adenoma.
- Deferiprone showed genotoxic effects in: mouse lymphoma cell TK+/- forward gene mutation assay, chromosomal aberration assay in Chinese Hamster Ovary and human lymphocytes, micronucleus test in naïve male mice bone marrow erythropoietic cells and iron-loaded and naïve male and female mice bone marrow. It is thus a positive transspecies genotoxin and considered to be a trans-species carcinogen, which implies a carcinogenic risk for humans. (It was negative only in the Ames test).
- Deferiprone is **potently** teratogenic in rats and rabbits with soft tissue and skeletal malformations at all doses tested (25 mg/kg/day low dose in rats and 10 mg/kg/day in rabbits). Embryoletality occurred at doses of 100 mg/kg/day.
- It is noted that considering the daily maximum human dose of (b) (4) mg/kg as indicated in the proposed labeling, the safety margin is very low based on body weight (5-8 times maximum human dose and MHD), and in most cases the multiple of the MHD based on surface area is less than 1.0.
- C<sub>max</sub> and AUC generally increased with dose. The rate of increase was greater in non-iron loaded animals.
- In single dose toxicity studies in naïve and iron-loaded rodents the maximum tolerated dose (MTD) was in the range of 500-800 mg/kg. Histopathology showed foci of cardiac and skeletal muscle necrosis.
- In 12-month repeat oral dose toxicity study at high doses (75 and 100 mg/kg bid) in naïve rats, iron removal resulted in iron deficiency anemia severe enough to cause death in some animals.
- In a repeat dose toxicity study deferiprone given orally to naïve cynomolgus monkeys at 75 mg/kg twice daily for 52 weeks did not show significant effects (NOAEL 150 mg/kg/day). In iron-loaded monkeys the NOAEL was 200/250 mg/kg/day. In a 3-month study 6 of 13 noniron-loaded monkeys died from treatment with 250 mg/kg/day for 18 days, due to drug induced iron deficiency anemia and resultant effects. No drug effects were seen at doses ≤100 mg/kg/day.
- Fertility, reproductive performance, fetal survival and development were not affected in male or female rats receiving up to and including oral deferiprone 150 mg/kg/day prior to and during gestation.

Review noted that lifetime carcinogenicity studies had not been conducted but the sponsor's proposal to conduct a 2-year carcinogenicity study in rats and a 6-month study in p53 knockout mice during Phase 4 is adequate. Pharmacology found the application

acceptable for approval with appropriate warnings in the product labeling regarding the genotoxicity and carcinogenic risk and fetal and developmental toxicity (Pregnancy Category C).

Clinical Pharmacology: Clinical Pharmacology and Biopharmaceutics review of the application was conducted by P. L. Hepp, Pharm.D. (3/27/08 and 9/24/09) and J. Grillo, Ph.D. (10/22/09). The Biopharmaceutics Reviewable Unit was submitted 9/26/07. Deficiencies were sent to the sponsor on 3/27/08 and responses were received on 6/27/08. studies included investigations of relative bioavailability, mass balance, food-effect, dose proportionality, multiple dose pharmacokinetics (PK)/ pharmacodynamics (PD), drug-drug interaction with digoxin, and cardiac safety (thorough QT study). Notable findings and conclusions from the 9/24/09 review included:

- No formal dose-ranging or optimization studies were conducted to determine exposure (i.e., C<sub>max</sub> and AUC)-response or exposure-safety relationship for Ferriprox.
- The major route of metabolism of deferiprone is UGT1A6 mediated 3-O-glucuronidation, and the major route of elimination is renal for both deferiprone and its glucuronide.
- In the fasted condition t<sub>max</sub> was 1.06 hr and t<sub>1/2</sub> was 1.90 hr.
- There was a 38% decrease in deferiprone C<sub>max</sub>, but no significant effect on AUC when the fed tablet treatment was compared to the fasting tablet treatment and the t<sub>max</sub> was delayed, suggestion a food effect on the rate but not the extent of absorption.
- Deferiprone pharmacokinetics was similar in β-thalassemia patients with cirrhosis (mild hepatic impairment) and those without cirrhosis. Deferiprone and its glucuronide were eliminated monophasically with a t<sub>1/2</sub> of approximately 2 hours.
- In thalassemia patients chronically receiving deferiprone, deferiprone accumulated about 30% beyond predicted value for linear pharmacokinetics.
- The effect of age, gender, race, renal impairment, and hepatic impairment have not been studied for deferiprone.
- Drug interactions for deferiprone have not been studied.
- A QT study has not been conducted for deferiprone.

The review found the application acceptable for approval with post-marketing requirements to: (1) conduct a pharmacokinetic study of both deferiprone and its primary 3-O-glucuronide metabolite in patients with hepatic impairment; (2) conduct a pharmacokinetic study of both deferiprone and its primary 3-O-glucuronide metabolite in patients with renal impairment.; (3) study the effect of deferiprone and its primary 3-O-glucuronide metabolite on the ECG QT interval in healthy volunteers. and (4) conduct two *in vitro* studies; one to determine the affect of moderate to strong UDP glucuronosyltransferase (UGT) inhibition and one to determine effect of moderate to strong UGT induction on the metabolism of deferiprone and determine if additional *in vivo* drug interaction studies are needed. Additional recommendations were provided for

study of deferiprone in obese patients, further study of single dose versus steady state PK, PK studies in pediatric patients, examination of effect of genotype (UGT1A6 polymorphisms) and suggestion was made that the applicant collect DNA in future studies and attempt to identify genetic or other biomarkers for agranulocytosis and other severe adverse events (e.g., arthropathy).

Division of Scientific Investigations (DSI) Inspection: Three foreign clinical investigator sites for Study LA 16-0102 were inspected. These included the cardiac MRI T2\* reading center. For these sites, the review found that, “Inspection findings documented adherence to Good Clinical Practices regulations governing the conduct of clinical investigations. No significant discrepancies were noted with the data listings provided in the NDA and source documents at the clinical sites. The data generated by these inspected sites appear reliable in support of the application.” (Clinical Inspection Summary, Dr. A. Orenca, 10/30/09).

For Study LA-01 the Summary states: “The inspection of Dr. Olivieri’s site (1) revealed some discrepancies in the hepatic iron concentrations between the sponsor’s data listings and the documents at Dr. Olivieri’s site, and where source documentation was available, Dr. Olivieri’s data appeared to be reliable, (2) there were data that the sponsor excluded from the 24-month completer analyses, that may not have been appropriate for exclusion, and (3) Dr. Olivieri did have documents at her site that suggested increased hepatic iron and/or hepatic fibrosis with chronic deferiprone therapy, although DSI was not able to verify the source for these values, and, in some instances, the fibrosis may have been confounded by coexistent hepatitis C infection and/or baseline fibrosis.” The report recommended that to address concerns of possible hepatic toxicity and waning efficacy, DMIHP could seek an independent third party inspection of the study site and/or have the sponsor conduct an additional long-term efficacy and safety study.

Advisory Committee: Discussion of the application at a meeting of the Oncologic Drugs Advisory Committee was planned for 10/6/09. However, because of findings in the preliminary reporting of results of the DSI inspection suggesting existence of data from the Toronto (Olivieri) study sites that may not have been fully reported in the NDA application, the decision was made to cancel the 10/6/09 ODAC meeting “to allow time for FDA to review and resolve several outstanding issues. The agency intends to continue evaluating NDA 021-825 and, as needed, may schedule an advisory committee meeting in the future.” (Federal Register, 74:50980 (Oct 2, 2009)).

Risk Evaluation and Mitigation Strategy (REMS): The sponsor has proposed a REMS. The Division of Risk Management (DRISK), Office of Surveillance and Epidemiology (OSE), has deferred defer comment on the Sponsor’s proposed REMS as review findings and discussions have made apparent that a Complete Response (CR) letter will be issued. A DRISK Memorandum (J. Weaver, 10/22/09) states that a final review on the appropriate risk management strategy for deferiprone will be provided after the Sponsor responds to the deficiencies in the CR letter and the risk-benefit profile can be re-

evaluated. DRISK recommends inclusion of the following comment in the CR letter: “Depending on the outcome of these analyses, FDA may require the submission of a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drug outweigh its risks. In your response to this letter, you may wish to resubmit the REMS submitted October 14, 2009.”

Other: Additional input for the application review was as follows:

- Proprietary name review found the name Ferriprox acceptable. The Division of Medication Error Prevention and Analysis (DMEPA) reconsidered an earlier objection to the name Ferriprox (that “Ferr” might imply that the drug is an iron supplement), considering the sponsor’s argument that the product already is marketed with that name in a number of countries without confusion and that distribution will be limited to certain specialty pharmacies and they anticipate that an REMS will be in place. (L. Holmes, 9/4/09)
- Division of Drug Marketing, Advertising and Communications (DDMAC) provided recommendations for the product labeling. (M. Safarik, 8/26/09)
- DMEPA provided recommendations for container and package insert labeling (J. Abdus-Samad, Pharm.D., 10/23/09).

#### **Conclusions and Recommendations:**

The sponsor is seeking approval of Ferriprox (deferiprone), an orally active iron chelator, for treatment of iron overload in patients with transfusion-dependent thalassemia and treatment of iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate.

The sponsor has failed to provide substantial evidence of effectiveness and safety in the submitted application. The drug development program for this application is particularly weak in that efficacy is claimed on the basis of a single, small, randomized, open label study (LA 16-0102) utilizing a primary efficacy endpoint (cardiac MRI T2\*) that has not been validated in other clinical trials and that lacks demonstration of clinical benefit or correlation of the T2\* measure with clinical outcomes in the submitted efficacy study. Importance of providing data on clinically meaningful endpoints for the NDA submission was emphasized in the FDA pre-NDA meeting with the sponsor on 10/9/01. Based on the design and results of the study, LA 16-0102 is insufficient to provide persuasive evidence of efficacy. The sponsor’s major supportive study (LA 12-9907) is a retrospective, examination of medical records and does not provide meaningful support for efficacy of deferiprone. At least one additional prospective, randomized, controlled study of adequate design and using a clinically accepted study endpoint such as biopsy measured change in liver iron concentration or important clinical outcomes is needed to establish the efficacy of deferiprone for the desired indications.

The application contains a second, larger randomized, controlled study (LA 01) designed to show that deferiprone is “similar” to deferoxamine in regard to change in LIC. The sponsor is not considering this study for demonstration of efficacy due to premature

termination of the major investigator and allegations of problems with study conduct and incompleteness of the data. Interestingly, the interim report of this study was submitted to support the approval of deferiprone by the European Medicines Evaluation Agency (EMA) in 1999. Information on patients treated in that study who were followed further after study discontinuation (from the literature and DSI investigation reports) suggests that long-term treatment with deferiprone may lead to yet uncharacterized liver injury.

The major clinical safety concern apparent in the trials and the European post-marketing experience is development of agranulocytosis. The sponsor has appropriately proposed a REMS for deferiprone, should it be marketed. Deferiprone also is potentially genotoxic and causes fetotoxic shown to cause soft tissue and skeletal malformations in animals. Literature publications raise a concern of possible liver toxicity with long-term use of the drug. This concern has not been addressed in the current application. Certain adverse reactions (e.g., neurological) may occur more frequently with excessive over-chelation of patients; hence, monitoring of patients for response to therapy is important.

In conclusion, the Ferriprox (deferiprone) NDA has major deficiencies that preclude approval at this time. The sponsor should be issued a Complete Response (CR) letter requiring that for approval the sponsor must do the following:

1. Conduct a confirmatory prospective, randomized, controlled, adequate-and-well controlled clinical study to evaluate efficacy of deferiprone with an efficacy endpoint of clinically meaningful morbidity and/or mortality. The study should be adequate in size to provide robust evidence of efficacy and meaningful comparative safety data. The study should enroll pediatric patients as well as adults to better reflect the characteristic of  $\beta$ -thalassemia.
2. If cardiac MRI-T2\* is to be used to demonstrate efficacy, provide persuasive evidence from clinical studies to identify and characterize a quantitative and qualitative correlation between change in T2\* values and clinically meaningful measures of cardiac function. The study protocol should be submitted to the Agency for review.
3. Provide additional data from prospective clinical followup of patients receiving deferiprone evaluating for possible hepatotoxicity.
4. Provide a more detailed report of the process and events surrounding the shut-down of the LA 01 Toronto Olivieri site, including a timeline. Provide a copy of the marketing application submitted for EMA approval of deferiprone in 1999.
5. Consider commissioning an independent investigation of the LA 01 Toronto sites to verify completeness and accuracy of collection of study data prior to site termination.

6. Examine and analyze the deferiprone safety database (including post-marketing) for occurrence of hepatic adverse reactions.
7. Provide revised labeling and REMS based on findings results of above studies and evaluations.
8. Clinical Pharmacology recommendations should be addressed.
9. Chemistry deficiencies also should be addressed.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	ORIG-1	AOPHARMA INC	FERRIPROX (DEFERIPRONE)

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/s/

KATHY M ROBIE SUH  
11/25/2009

## Summary Review for Regulatory Action

<b>Date</b>	November 18, 2009
<b>From</b>	Dwayne Rieves, MD
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b> <b>Supplement #</b>	21-825
<b>Applicant Name</b>	ApoPharma, Inc.
<b>Date of Submission</b>	January 29, 2009
<b>PDUFA Goal Date</b>	November 30, 2009
<b>Proprietary Name /</b> <b>Established (USAN) Name</b>	Ferriprox (Deferiprone film-coated tablets)
<b>Dosage Forms / Strength</b>	500 mg tablets
<b>Proposed Indication(s)</b>	1. "for the treatment of iron overload in patients with transfusion dependent thalassemia; 2. the treatment of iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate."
<b>Action/Recommended Action for NME:</b>	Complete Response

<b>Material Reviewed/Consulted</b> OND Action Package, including:	<b>Names of discipline reviewers</b>
Medical Officer Review	George Shashaty, MD
Statistical Review	Satish Misra, PhD/Jyoti Zalkikar, PhD
Pharmacology Toxicology Review	David Bailey, PhD/Adebayo Laniyonu, PhD
CMC Review/OBP Review	William Adams, PhD/Ravi Harapanhalli, PhD
Microbiology Review	Not applicable
Clinical Pharmacology Review	Joseph Grillo, PhD/Young Moon Choi, PhD
DDMAC	Michelle Safarik, PA-C
DSI	Anthony Orenca, MD/Tejashri Purohit-Sheth, MD
CDTL Review	Kathy Robie Suh, MD, PhD
OSE/DMEPA	Jibril Abdus-Samad, PharmD/Todd Bridges, RPh
OSE/DDRE	Not applicable
OSE/DRISK	Mary Dempsey/Joyce Weaver PharmD
Pediatric/Maternal Health	Alyson Karesh, MD/Hari Sachs, MD

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DSI=Division of Scientific Investigations

DDRE= Division of Drug Risk Evaluation

DRISK=Division of Risk Management

CDTL=Cross-Discipline Team Leader

## **Signatory Authority Review Template**

### **1. Introduction**

Deferiprone (Ferriprox), an oral iron chelator, is proposed for marketing as a treatment for iron overload in two patients populations, as highlighted in the header (above). The application was a "rolling" submission in which portions were received over several years. The final portion (clinical) was submitted in January, 2009 and triggered this first, full review cycle.

FDA scheduled deferiprone for a discussion at the October 6, 2009 meeting of the Oncology Drugs Advisory Committee. However, approximately two weeks prior to this meeting, a deferiprone investigator (Nancy Olivieri, MD) from the University of Toronto met with the review team and expressed concerns about the NDA data. This meeting had been requested by Dr. Olivieri who was acting independently from the NDA applicant. At this meeting, Dr. Olivieri provided statements and documents that appeared inconsistent with the information submitted by the DNA applicant. Approximately one week prior to the advisory committee, the review team received a report from FDA's inspection of Dr. Olivieri's site. This inspectional report maintained that Dr. Olivieri was generally consistent with the expectations of Good Clinical Practice (GCP), a finding that differed from the NDA applicant's contention that Dr. Olivieri's site was non-GCP compliant.

The information provided by Dr. Olivieri and FDA inspectional findings were particularly notable in that Dr. Olivieri cited safety concerns with deferiprone, including an increased risk for death (compared to deferoxamine, another iron chelation drug). Additionally, one of the studies (Study LA-01, in which Dr. Olivieri's site had been terminated) was potentially a major safety and efficacy study. Indeed, Study LA-01 was the largest sample size study in the NDA portfolio--71 patients--and used an efficacy endpoint that FDA has previously accepted as indicative of clinical benefit.

Based upon the inconsistencies among the NDA applicant's supplied clinical data, FDA inspectional findings and the information supplied by Dr. Olivieri, FDA canceled the October advisory committee in order to obtain further clarification of the safety and efficacy data. Specifically, FDA is requesting verification that deferiprone does not pose a mortality or important liver toxicity risk and that the drug is effective in iron elimination over a multi-year period. This review cycle also disclosed deficiencies in manufacturing which will also be conveyed to the sponsor in the Complete Response letter.

### **2. Background**

The marketed iron chelator drugs consist of deferoxamine (a parenteral) and deferasirox (tablets for oral administration). Deferasirox (Exjade) was approved under the accelerated

approval pathway in 2005 based upon a 600 patient, randomized controlled study in which the drug was shown to lower serum ferritin and liver iron content despite the continued administration of blood transfusions to patients. Deferoxamine (a drug approved many years ago), the comparator in this study, lowered serum ferritin and liver iron content in a similar pattern.

Deferiprone was initially studied in clinical trials sponsored by academicians (no corporate sponsor). Subsequently, ApoPharma assumed responsibility for the drug development. In exploratory studies, deferiprone was shown to chelate iron in a manner that enhanced elimination of iron from the body. Subsequent clinical studies focused upon alterations in serum ferritin, changes in liver iron content and changes in cardiac iron content (as measured by magnetic resonance imaging T2\* quantification). The drug has been marketed in Europe for several years as a "second line" (after deferoxamine) form of iron chelation.

The deferiprone clinical development program has been complicated by disagreements between a site investigator (Dr. Nancy Olivieri/University of Toronto) and ApoPharma. The company submitted the application citing a single clinical study as the source of data confirming deferiprone safety and efficacy. This study (Study LA16-0102) assessed cardiac T2\* changes over a one year period of time (deferiprone compared to deferoxamine). The applicant did not propose any other studies as sufficient for hypothesis-testing confirmation of deferiprone effects. The applicant specifically cited Study LA-01 as deficient, based upon problems with Dr. Olivieri's clinical site. As described below, inconsistencies between the applicant's data and information at Dr. Olivieri's site importantly impacted this review cycle.

Study 16-0102, the applicant's proposed single confirmatory study, assessed clinical effects upon MRI changes in cardiac iron content and ejection fraction. The MRI measure of iron content, T2\*, has not been previously accepted by FDA as a reliable indicator of cardiac iron, although accumulating published data generally support its usefulness. The clinical meaningfulness of cardiac T2\* data remains unsettled and was a topic planned for focused discussion at an advisory committee.

Exclusive of the clinical data challenges, other substantive review issues pertained to manufacturing deficiencies.

### **3. CMC/Device**

I concur with the conclusions reached by the chemistry reviewer regarding the unacceptability of the manufacturing of the drug product and drug substance. The deficiencies include problems within a drug master file. Manufacturing site inspections were completed and disclosed deficiencies at one site. The complete response letter will describe the manufacturing deficiencies

### **4. Nonclinical Pharmacology/Toxicology**

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. The reviewer noted a need for the conduct of carcinogenicity studies following market approval of the drug.

## 5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. However, the reviewer had multiple recommendations for post-approval pharmacology studies. These requests will need to be revisited during subsequent review cycles.

## 6. Clinical Microbiology

Not applicable.

## 7. Clinical/Statistical-Efficacy

Dr. George Shashaty provided the clinical review and Dr. Satish Misra, the statistical review. Both reviewers expressed concern about the sufficiency of the supplied data (both recommended non-approval).

The applicant proposed Study LA 16-0102 as the single providing confirmatory evidence of safety and efficacy. This study and results are briefly summarized below. Following this study summary, I cite some of the information pertaining to the review findings that have resulted in uncertainty regarding the "data completeness" of the submitted clinical study reports, particularly with respect to the clinical study sites supervised by Dr. Nancy Olivieri.

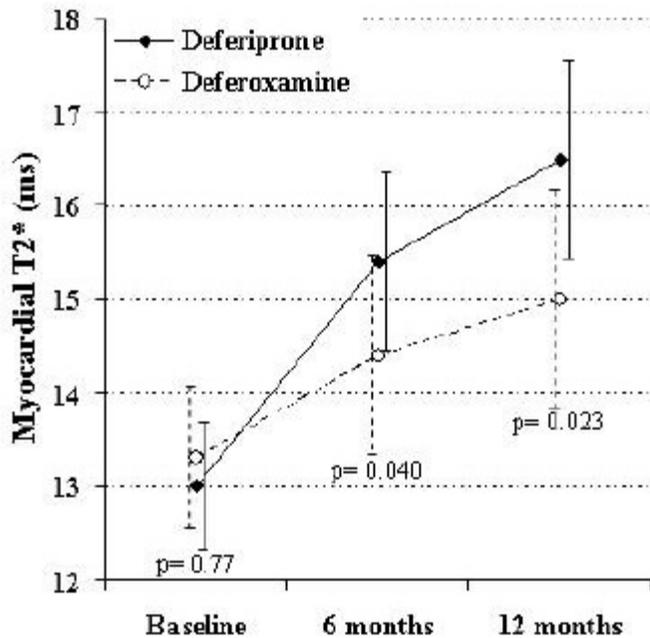
### *Highlights of Study LA 16-0102, the single study proposed to support efficacy:*

**Study LA 16-0102** was an open-label, randomized, active-control, parallel group, multi-center trial that sought to determine whether the oral administration of deferiprone for 12 months exhibited superior efficacy in removing excess iron from the heart as reflected by changes in cardiac magnetic resonance T2\* (CMR T2\*) when compared to standard subcutaneous infusions of deferoxamine.

Twenty-nine patients with  $\beta$ -thalassemia and transfusional hemosiderosis were randomized to receive deferiprone at a dose of 100 mg/kg/d and 32 patients were randomized to receive deferoxamine at a dose of 50 mg/kg/d for 5-7 days per week. Five patients did not complete the trial (2 in the deferiprone arm and 3 in the deferoxamine arm). The primary analysis was performed on the intention-to-treat (ITT) population. For patients assigned to receive deferiprone, the geometric mean value of the MRI T2\* increased from 13.03 milliseconds (ms) at baseline to 16.51 ms at the end of the study, while corresponding values for patients

receiving deferoxamine increased from 13.32 ms to 15.01 ms. The difference in change in T2\* between the two treatments was statistically significant (p=0.02, based upon the sponsor's chosen analytical method/which was verified by nonparametric testing). When interpreting the study's primary endpoint, one must consider that the analytical plan cited the use of a form of a t-test statistical method, "if the data were normally distributed." Indeed, the final primary endpoint data were not normally distributed. The analytical plan has stated that "nonparametric tests" were to be performed in this situation, although the specific statistical tests were not identified. The sponsor chose a methodology that relied on a log transformation of the data. FDA's non-parametric analyses verify the statistical success for the primary endpoint result. However, the relatively small sample size of this study importantly limits its ability to confirm efficacy (for example, the sample size precluded subset analyses).

Below is a copy of the sponsor's figure that summarizes the changes in cardiac T2\*.



Even with apparent statistical success upon the primary endpoint, the clinical meaningfulness of the cardiac T2\* changes is unclear. To address this concern, the applicant supplied summary information from studies performed by Dr. Dudley Pennell and colleagues in the United Kingdom. These summary data report positive correlations between human cardiac iron content (autopsy samples) and *ex vivo* MRI T2\* measurements (for iron-overloaded hearts). Additionally, the applicant submitted summary information from a long-term follow-up program of 652 thalassemia major patients in the UK who underwent baseline MRI T2\* assessments and were followed for clinical outcomes. These data appeared to indicate that the lower the cardiac MRI T2\* value, the higher is the risk for developing iron-induced cardiac failure. No data were supplied to show that incremental changes in T2\* actually resulted in a clinical benefit. Hence, the clinical meaningfulness of changes in cardiac MRI T2\* remain unclear. Data are necessary to verify this clinical meaningfulness.

Study LA 16-0102 also included assessments of serum ferritin and liver iron content (by SQUID). Serum ferritin values decreased (from baseline to end of study) in both treatment groups with no statistical difference between the groups. Liver iron changes (from baseline to end of study) were similar between the study groups (no statistical difference), although the point estimate favored deferoxamine. In exploratory analyses of changes from baseline to end of study within each study group, only the deferoxamine group attained nominal statistical significance for a decrease in liver iron concentration.

***Highlights of "Data Completeness" Concerns that Appeared Shortly Before the Scheduled October, 2009 Advisory Committee:***

On September 16, 2009 Dr. Nancy Olivieri met with the FDA review team (the team did not solicit this meeting/instead, the team agreed to the meeting based upon Dr. Olivieri's request). At this meeting, Dr. Olivieri indicated that she suspected the information within the NDA was incomplete and potentially misleading, mainly due to ApoPharma actions at her clinical site.

Specifically, Dr. Olivieri noted that she had been informed by the company that she was noncompliant with Good Clinical Practice expectations with respect to a major clinical study (Study LA-01, conducted from 1993 to 1996). Indeed, the LA-01 study report (within the NDA) noted that Dr. Olivieri's participation in this study had been terminated (Dr. Olivieri was the study's principal investigator). At the September meeting, Dr. Olivieri left several volumes of information that made multiple contentions, as follows:

"My analysis of LA-01, of LA-03 and later scientific data yields four areas of concern in relation to the efficacy and safety of deferiprone. These concerns, presented at greater length in the Summary and in the forthcoming Appendices, include:

- 1/ acceleration of hepatic fibrosis
- 2/ inadequate control of body iron burden
- 3/ emergence of cardiac disease during deferiprone exposure
- 4/ deaths in the Toronto deferiprone-treated patients."

The supplied information consisted of multiple publications, documentary upon the publications, tabular summaries of individual patient information and summaries of audit findings.

Dr. Oliveri's statements to the FDA in the September 16, 2009 meeting were generally inconsistent with information supplied by the applicant, particularly with respect to Study LA-01. This study (as described in the applicant's study report) was a randomized comparison of deferiprone to deferoxamine in 71 patients with iron overload. The patients were to be followed for at least two years and assessed for changes in liver iron content (primary endpoint) and serum ferritin (secondary endpoint). The patients were also to undergo a third year of follow-up "during which safety and efficacy would continue to be monitored" (study report).

The Study LA-01 report noted, "During the third year of the study, ApoPharma terminated the study at the sites in Toronto due to irreconcilable differences and ongoing problems with the principal investigator, which included the failure to meet the obligations outlined in the Drugs Directorates guidelines on "Conduct of Clinical Investigations", and the sponsor's concern regarding the safety of patients." The study report further cites the extent of missing liver iron content data and serum ferritin values, mainly at Dr. Olivieri's clinical site.

Using the available Study LA-01 data, the study report noted, "The data from this randomized, controlled study indicate that deferiprone is as effective as deferoxamine in controlling body iron load in transfusion-dependent patients...There was also no indication that deferiprone therapy resulted in a change in liver enzyme levels that was different from what was observed with deferoxamine, as shown by the bi-monthly ALT measurements. The results of this study support the indication of deferiprone for the treatment of iron overload in transfusion-dependent patients."

The report further notes that, "In addition, the investigator at the Toronto sites failed to schedule a total of 65 (deferiprone 27, deferoxamine 38) patients for either their annual, early termination or study completion LIC (liver iron concentration) assessments according to protocol. The end result was that some patients were assessed more frequently than others, not all patients were assessed within the expected time frame of their annual assessment date."

The Study LA-01 report within the NDA does not describe the safety problems cited by Dr. Olivieri.

As a component of the routine NDA clinical site inspectional process, the division requested inspection of Dr. Olivieri's site/Study LA-01. This request was based upon published reports by Dr. Olivieri that suggested deferiprone caused hepatic fibrosis and was ineffective as a long term treatment for iron overload (NEJM/multiple citations, e.g., 342:1539; 348:860; 339; 417). The inspection of Dr. Olivieri's site was requested, in part, to help obtain verification of the applicant's contentions that the site investigator was non-compliant with expectations of Good Clinical Practice.

The FDA inspectional report noted that, when the field inspector compared the data listings prepared in the assignment to the field office against the data summaries prepared by Dr. Olivieri's clinical site this..."raised a number of questions regarding the sponsor's criteria for inclusion and exclusion of data..." in the data listings for hepatic iron concentration data that were submitted with the NDA. The inspectional report notes that, "Specifically, the sponsor's data set excludes in their entirety...29 of 64 treated subjects." The report notes that the field inspector subsequently modified the FDA report to correct numerical errors/specifically to state that the data were missing for 23 of 63 treated subjects. Nevertheless, the inspectional reports notes that "The rationale for the exclusion of the data in the table below appears to have been inconsistently applied by the sponsor." Overall, the FDA field inspector's findings indicated that the sponsor may not have submitted all applicable data from Dr. Olivieri's site.

Additionally, the FDA inspectional report found that the applicant had excluded liver outcome data from the Study LA-01 report (information applicable to the occurrence of hepatic

fibrosis). The inspectional report also cites some concerns with Dr. Olivieri's site, particularly with respect to the unavailability of source documents that verified liver iron content values. The overall FDA inspectional finding was that "Dr. Olivieri's site appeared to be in general compliance with Good Clinical Practice; however, this assessment is based on a review of a limited number of records for assessment of GCP compliance."

Based upon the information highlighted above, FDA chose to cancel the October advisory committee and further review the applicant's data, in the broader context of Dr. Olivieri's assertions and the FDA inspectional findings.

The available data and information (from comparisons of NDA data to FDA site inspectional findings and to the communications from Dr. Olivieri) preclude the review team from concluding that the full clinical data from Study LA-01 were submitted to the NDA. This deficiency also applies to the other studies in which Dr. Olivieri participated.

During the review, no concerns were evidenced regarding the data integrity and thoroughness for Study LA 16-0102, the phase 3 confirmatory study that was cited by the applicant as the major study assessing deferiprone efficacy and safety.

## **8. Safety**

As previously noted, Dr. Nancy Olivieri presented the review team with information that suggested deferiprone therapy increases the risk for liver fibrosis and death. The liver fibrosis risk was cited in a publication she authored (NEJM 1998; 339: 417-23). The review of data submitted to the NDA signaled a liver toxicity concern (enzyme elevation) within the main confirmatory study, although "fibrosis" was not specifically identified as the toxic event. Additionally, the main confirmatory study data did not provide a mortality risk signal. However, the NDA findings are compromised by the uncertainty pertaining to NDA data "completeness." As noted above, a question of data "completeness" was a fundamental finding from this review cycle.

Exclusive of the safety problems cited by Dr. Olivieri, the most prominent deferiprone safety concerns pertained to agranulocytosis and liver enzyme elevations. Randomized, comparative clinical trial safety data are limited to Study LA-16-0102. All other studies were generally observational in nature, used cross-over designs or studied deferiprone drug regimens not proposed for marketing. Safety data were not collected in the major supportive study (Study LA-12-9907).

No agranulocytosis was reported in Study LA-16-0102; alanine aminotransferase increases reported as adverse events occurred in 38% of the deferiprone group and 13% of the deferoxamine group. One event was assessed as serious (deferiprone group) but was also related to acute Cytomegalovirus infection.

Deferiprone has been marketed in Europe since 1999 and, in the post-marketing experience, the applicant reports that 11 deaths have followed the development of agranulocytosis.

The applicant proposed a label that described a requirement for weekly measurement of the absolute neutrophil count in order to try to minimize the risk for agranulocytosis. The proposed label also outlined a requirement for monthly measurement of ALT values with directions that [REDACTED] (b) (4)

To address the liver toxicity and agranulocytosis concerns, the sponsor submitted a draft Risk Evaluation and Mitigation Strategy (REMS). However, the REMS was not reviewed during this cycle due to the inability to verify the "completeness" of the data submitted to the NDA. Incomplete data submission precludes a thorough characterization of deferiprone safety.

## **9. Advisory Committee Meeting**

As noted above, the October, 2009 advisory committee for deferiprone was canceled due to the detection of "data completeness" problems shortly before the meeting. Insufficient resolution of these problems would have compromised the usefulness of advice obtained from the committee. Hence, the review team elected to cancel the advisory committee.

## **10. Pediatrics**

Deferiprone has an "orphan drug" designation from the FDA. Hence, the PREA expectations do not apply. In the clinical development program, 111 pediatric patients (aged 6 to 16 years) were exposed to deferiprone; safety findings appeared similar to those from older patients. In general, additional pediatric patient exposure is important to help characterize the safety and efficacy of deferiprone.

## **11. Other Relevant Regulatory Issues**

The DSI report cited several items of particular relevance to the concern about "data completeness."

## **12. Labeling**

Not addressed in this review cycle.

## **13. Decision/Action/Risk Benefit Assessment**

Overall, three major issues arose during this review cycle:

- 1) The unclear clinical meaningfulness of changes in cardiac MRI T2\* values and the relatively small samples size for Study LA-16-0102. The single clinical study proposed to

support deferiprone efficacy used changes in cardiac MRI T2\* as the evidence of clinical benefit. However, data were not supplied to the NDA that verified the clinical meaningfulness of incremental changes in cardiac T2\*. Additionally, the study was too small in sample size to allow its use as the single study supporting deferiprone efficacy.

2) The inability to verify that complete data (particularly safety data) were supplied to the NDA. This finding was based upon discordance between the FDA inspectional findings at a clinical site in Toronto, CA and the data supplied to the NDA. The FDA inspector's findings indicated some clinically applicable data were available at the Toronto site but were not submitted to the NDA.

3) Insufficient manufacturing information.

These issues form the basis for the Complete Response letter. This letter will generally cite the need to:

- obtain data that verifies the completeness of information submitted for Study LA-01. This could be addressed through a third part reconstruction of the database or complete audit of the source data as it applies to the data submitted to the NDA. This need is based on the FDA inspectional findings.
- provide data that verify deferiprone therapy is not associated with a mortality disadvantage, particularly with respect to the occurrence of liver fibrosis and the potential lack of iron elimination efficacy when the drug is administered over a prolonged period of time. These data could potentially be derived from follow-up mortality data from subjects who participated in Study LA-01 (conducted between 1993 and 1996); if these data are not available, then additional clinical studies are likely necessary. This need is based upon the published report of liver fibrosis, the evidence of a liver safety signal in Study LA 16-0102 and the minimal amount of pediatric exposure data within the application. Pediatric exposure information is important because these patients would likely have the greatest cumulative risk for liver problems due to the life-long need for chelation therapy.
- provide data verifying the clinical meaningfulness of cardiac MRI T2\* and additional controlled data that verify efficacy.
- resolve the manufacturing deficiencies, including issues related to a drug master file and facility inspectional issues.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	ORIG-1	AOPHARMA INC	FERRIPROX (DEFERIPRONE)

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RAFEL D RIEVES  
11/20/2009

## CLINICAL REVIEW

Application Type Standard  
Application Number(s) 21825  
Priority or Standard Standard

Submit Date(s) January 28, 2009  
Received Date(s) January 29, 2009  
PDUFA Goal Date November 30, 2009

Reviewer Name(s) George Shashaty  
Review Completion Date October 19, 2009

Established Name Deferiprone  
(Proposed) Trade Name Ferriprox  
Therapeutic Class Iron Chelator  
Applicant ApoPharma

Formulation(s) Tablets  
Dosing Regimen 25 mg/kg three times daily  
Indication(s) Iron overload  
Intended Population(s) Thalassemia major

## **List of Abbreviations**

ADR	Adverse drug reaction
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CHF	Congestive heart failure
CMR	Cardiac magnetic resonance
EMEA	European Medicines Agency
Hgb	Hemoglobin
IND	Investigational new drug
ITT	Intent to treat
LIC	Liver iron concentration
LOCF	Last observation carried forward
LVEF	Left ventricular ejection fraction
LVSF	Left ventricular shortening fraction
MS	Millisecond
NDA	New drug application
NYHA	New York Heart Association
OC	Observed cases
PP	Per protocol
SQUID	Sequential quantum interference device

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

Deferiprone should not be approved for marketing in the United States for the following indications:

- (1) for the treatment of iron overload in patients with transfusion-dependent thalassemia, and
- (2) for the treatment of iron overload associated with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate.

This recommendation is made on the basis of the data submitted to the NDA by the sponsor. The deficiencies upon which this recommendation is made include the following:

- The support for the application is based on a single adequate and well-controlled trial (LA 16 0102), and this trial does not conform to the following requirements for approval based on such a trial:
  - The trial consisted of only 61 patients and only 29 were treated with deferiprone.
  - Fifty-six of the patients were enrolled from only two institutions (although one of the institutions was said to have two separate departments).
  - Analyses of secondary endpoint results of the trial did not provide evidence of a decrease in serum ferritin or in liver iron concentration, endpoints which were most often accepted as evidence of efficacy at the time that the trial was performed.
  - The statistical results were not robustly persuasive.
- The primary endpoint of the trial, a change in cardiac MRI T2\* (believed to reflect iron content in the heart) from baseline to the end of twelve months of therapy, is a surrogate endpoint. The sponsor has failed to provide evidence of the relationship between the increase in T2\* (and the degree of increase in that is needed) required to predict clinical benefit on mortality or morbidity in patients with transfusion dependent hemosiderosis. In the study, the mean change in MRI T2\* was  $3.9 \pm 3.6$  milliseconds for patients treated with deferiprone compared to  $2.3 \pm 3.6$  milliseconds for patients treated with the approved active comparator, deferoxamine.
- The measurement of MRI T2\* has never been previously used as an efficacy endpoint for a phase 3 study to support an NDA approval.
- The age range of patients enrolled in the trial was from 18 to 36 years of age. No pediatric patients were enrolled, and it is in pediatric patients in whom a large fraction of the use of deferiprone is likely to occur.
- Patients enrolled in the trial were required to have a baseline MRI T2\* of between 8 and 20 milliseconds. This eliminated more than half of thalassemia patients who were transfusion dependent and are likely to be recipients of deferiprone, if approved.

- The small increases in left ventricular ejection fraction and left ventricular shortening fraction which were secondary endpoints of the trial are of uncertain clinical meaningfulness because they occurred in patients with normal values at baseline.
- Adverse reactions were more common in patients treated with deferiprone (increase in alanine aminotransferase in 38%, T wave inversions in 17%) compared to deferoxamine (increase in alanine aminotransferase in 13%, T wave inversions in 0%).
- The main supportive study submitted by the sponsor (LA 12 9907) contained the following deficiencies:
  - It was retrospective in design.
  - The endpoint (occurrence of cardiac disease) was not well defined. My analysis of the data provided by the sponsor indicates that many of the patients who were said to have developed heart disease did not have a clinical basis upon which to make such a diagnosis.
  - Demographic characteristics were different between the deferiprone and the deferoxamine treated patients, particularly age at entry into the study and age at start of chelation, both of which may have biased the results in favor of deferiprone.
- The additional supportive data submitted by the sponsor cannot be used to determine the true efficacy and safety of the use of deferiprone for transfusion dependent hemosiderosis because they are either retrospective in design, contain only small numbers of patients, are uncontrolled, have variable results or contain data of uncertain integrity.
- Agranulocytosis occurred in 1.6% of 590 patients enrolled in clinical trials but no patients died from sepsis. In postmarket reports since the original approval of deferiprone in the European Union in 1999, there have been 83 cases of agranulocytosis, including 13 deaths from sepsis. The development of agranulocytosis is unpredictable.
- In pooled clinical trials, serum alanine aminotransferase levels were elevated to >2x ULN in 13% of patients treated with deferiprone compared to 3% of patients treated with deferoxamine. In early studies with deferiprone, there appeared to be an increase in fibrosis in the liver in patients treated with deferiprone. The sponsor has not performed any additional clinical trials to determine the frequency and clinical significance of this signal.
- Gastrointestinal adverse reactions are common with the administration of deferiprone. Data from clinical trials and postmarket reports indicate other safety concerns that relate to the development of arthropathy, pancreatitis, dermatological reactions, thrombocytopenia, Henoch-Schoenlein purpura and torsade-de-pointes. Overdosing with deferiprone appears to be associated with the development of various neurological symptoms.
- Virtually all of the patients enrolled in clinical trials conducted by the sponsor had thalassemia as the base diagnosis that led to the requirement for chronic transfusion therapy. The only patients with non-thalassemic anemias requiring chronic transfusion therapy were enrolled in LA 04, a Compassionate Use Treatment Protocol. LA 04 included 10 patients with myelodysplastic syndrome, 4 patients with myelofibrosis, 3 patients with sickle cell anemia and 1 patient each with a wide assortment of other base

diagnoses. Therefore, LA 04 does not provide sufficient data to evaluate the efficacy or safety of the use of deferiprone in patients whose anemia is not due to thalassemia. In order for the sponsor to gain approval for the marketing of deferiprone for the proposed indications, the sponsor needs to provide the following:

- Adequate and well controlled trials that demonstrate the clinical efficacy of the use of deferiprone using generally accepted clinical endpoints such as changes in liver iron concentration, diminution in serum ferritin levels, improvement in clinically important endpoints (congestive heart failure, hepatic dysfunction, diabetes, death). Assessment of additional secondary endpoints would also be useful.
- Adequate and well controlled trials might include a placebo control or an active comparator control (deferasirox might be an optimal comparator).
- Follow-up data from patients originally enrolled on the LA 16 0102 trial to establish whether or not the improvement in MRI T2\* led to an improvement in mortality and clinically important morbidity in patients treated with deferiprone compared to those treated with deferoxamine.
- Follow-up data from patients enrolled in the LA 12 9907 registry to determine whether or not the patients who were diagnosed with “cardiac disease” suffered a worse long term outcome compared to those who were not so diagnosed.
- If the sponsor wishes to have the Agency continue to evaluate indication #2 above, the sponsor must submit evidence that deferiprone therapy is safe and effective in those non-thalassemic populations for whom the indication is directed.
- Performance of a formal QTc study.
- Performance of a study to determine the long term effects of deferiprone on histological changes in the liver.
- All proposed studies should be submitted to the Agency for review and recommendations.

## 1.2 Risk Benefit Assessment

Transfusion dependent hemosiderosis in thalassemia patients is a severe disease. Iron overload occurs when blood is transfused (hemosiderosis). Each unit of packed red blood cells contains approximately 225 mg of iron. Since total body iron in the normal adult is between 3,000-5,000 mg (including all iron in circulating red cells, the liver and other reticulendothelial tissues, and in muscle), the transfusion of as little as 20 units of blood may lead to a doubling of total body iron because there are no means to increase its excretion. When present in excess, iron deposits in a number of body organs, particularly including the liver, heart and endocrine organs. Deposition of excess iron leads to dysfunction and eventual failure of these organs. Early death due to cardiac disease occurs in approximately 70% of these patients. Additionally, other morbidities are related primarily to excess iron deposition in the liver, pancreas or endocrine organs.

Iron chelation therapy is based on the ability of the chelator to bind to iron in the blood or organs of deposition with the subsequent excretion of the bound complex in the urine or feces. The original chelator, deferoxamine, was approved for use in 1968, and 40 years of use has supported its efficacy and safety. However, difficulties with its administration (the need for subcutaneous or intramuscular injection with the use of a pump over many hours on an almost daily basis) have limited compliance with therapy. In 2005, Exjade (deferasirox), an oral iron chelator received accelerated approval for the treatment of hemosiderosis due to chronic transfusion therapy for anemia in patients two years of age and older on the basis of data that showed a diminution in liver iron concentration (LIC) after treatment for one year. In clinical trials and in postmarketing reports, deferasirox appears to be associated with hepatic, renal, gastrointestinal, dermatological, hematological, ophthalmological, auditory and hypersensitivity adverse reactions.

The sponsor has submitted a New Drug Application (NDA) for Ferriprox® (deferiprone) for the treatment of iron overload: 1) in patients with transfusion-dependent thalassemia and 2) associated with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate. Deferiprone was first administered to humans in 1987 and early work was the product of academic efforts. Commercial development was slow and the drug was acquired by the current sponsor in 1993. Deferiprone was first approved in the European Union in 1999 and has the indication for “the treatment of iron overload in patients with thalassemia major when deferoxamine therapy is contraindicated or inadequate”. The statement from the Committee for Proprietary Medicinal Products at the time of approval indicated that marketing authorization should be granted “under exceptional circumstances because in the present state of scientific knowledge, comprehensive information on the safety and efficacy of the medicinal product cannot be provided”. Deferiprone is currently approved in 60 countries, in almost all of which the indication is as stated in the indication statement noted above.

The efficacy of deferiprone as a clinically useful iron chelator is suggested by its presumed mechanism of action, its use over 10 years in many countries in the world and by some of the studies performed by the sponsor or independent investigators. However, data to definitively support its efficacy and safety have not yet been provided by the sponsor. The single adequate and well controlled trial submitted by the sponsor appears to be a hypothesis generating study that uses a previously unevaluated surrogate endpoint instead of a clinically meaningful endpoint to determine efficacy. Supportive studies submitted by the sponsor are inadequate to definitively support the efficacy or safety of the use of deferiprone for reasons discussed previously. Therefore, the uncertainty of the clinical efficacy of deferiprone, combined with the known and potential adverse reactions of agranulocytosis and hepatic injury and other less common or less well documented adverse reactions, weigh heavily against the benefit/risk assessment of the drug.

### **1.3 Recommendations for Postmarket Risk Management Activities**

Not applicable.

## 1.4 Recommendations for Postmarket Studies/Clinical Trials

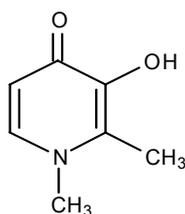
Not applicable.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Iron overload (hemosiderosis) is a clinical disorder that develops in persons who receive transfusion therapy for lifelong or chronic anemic syndromes. Iron from the transfused red cells is not eliminated from the body because the body is extraordinarily limited in its ability to excrete iron, which is usually avidly conserved. With repeated transfusion over time in these individuals, the ability to store the excess iron in the usual reticuloendothelial sites is overwhelmed, leading to deposition of iron in other body tissues. For some organs, notably the heart, liver, pancreas and endocrine system, iron deposition often leads to organ failure. In persons with hemosiderosis, the leading causes of death include cardiac and hepatic failure.

Deferiprone (L1, Ferriprox<sup>®</sup>) is an oral iron chelator that has been under study for more than 20 years, initially developed by independent clinical investigators seeking an alternate iron chelator to the then-only approved iron chelator, deferoxamine. Deferiprone was first administered to humans in the United Kingdom in 1987. Ciba-Geigy was its original commercial developer, but interest in development flagged and the drug was acquired by its present sponsor, ApoPharma, in 1993. Deferiprone is a new molecular entity with the chemical name of 1,2-dimethyl-3-hydroxypyrid-4-one. Its formula is as follows:



The sponsor's proposed indication is (1) for the treatment of iron overload in patients with transfusion-dependent thalassemia, and (2) for the treatment of iron overload associated with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate. The oral dose of deferiprone is 25 mg/kg administered 3 times daily (total daily dose of 75 mg/kg/d). The sponsor does not indicate any restriction of treatment based on age.

## 2.2 Currently Available Treatments for Proposed Indications

There are two currently approved treatments for the proposed indication as follows:

- Deferoxamine (Desferal<sup>®</sup>). Deferoxamine was approved in the United States in 1968 and its indication is for “the treatment of acute iron intoxication and of chronic iron overload due to transfusion-dependent anemias”. The approval of the drug was based on an understanding of its mechanism of action and uncontrolled studies that suggested its efficacy for the indication. Until the arrival of deferasirox, no other iron chelator was available. The drug is difficult to administer because it must be given parenterally (usually subcutaneously) over an extended number of hours (because of its short half-life) for between 5-7 days each week. As a result, compliance with therapy is often poor.
- Deferasirox (Exjade<sup>®</sup>). Deferasirox received accelerated approval in the United States in November, 2005 and its indication is for “the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older”. Approval was based on the demonstration of its efficacy in lowering liver iron concentration (LIC) based on liver biopsy in patients with transfusion related hemosiderosis.

## 2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient is not currently available in the United States.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Safety issues that have been noted with drugs in the same pharmacological class include:

- Deferoxamine. Auditory and visual disturbances; infections at the sites of administration; growth retardation; and infections with yersinia and mucor.
- Deferasirox. Hepatotoxicity; renal toxicity; dermatological disorders; auditory and visual disturbances; gastrointestinal toxicity; various cytopenias; and hypersensitivity reactions.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

There has been an abundance of regulatory activity associated with the clinical development of deferiprone. Important clinical interactions between the sponsor and the Division are summarized below.

- July 15, 1994. Original submission of the IND (IND 45724) for the use of deferiprone to treat iron overload. Apotex had licensed the rights to deferiprone in 1993.
- October 9, 2001. Pre-NDA meeting. The Division indicated that the safety data appeared to be sufficient to file an application, but the adequacy of the data for product approval was a review issue. The Division expressed concern about the development of neutropenia/agranulocytosis, the high rate of patient withdrawals and studies that appeared to be terminated early without explanation. The Division requested that all foreign post-marketing experience be submitted in the NDA as well as a description of

the content and format of regulatory submissions to other countries, particularly highlighting any differences from the U.S. submission. The Division indicated that data regarding the efficacy and safety of the use of deferiprone in patients with hemosiderosis due to conditions other than thalassemia major would have to be submitted if the sponsor wished to include such patients in the indication. The Division did not agree with the sponsor's plan not to perform some of the required non-clinical studies because the agent had been administered to many humans. In response to the sponsor's question regarding the sufficiency of the then-available data to support approval of the drug, the Division stated that the current efficacy database did not appear to be strong and did not satisfy the regulatory requirements for adequate and well-controlled trials, and that if what had been submitted in the background package represented all available data, the sponsor should submit efficacy and safety data from historical populations. The Division stated that efficacy endpoints would have to be linked to clinical improvement and that serum ferritin would have to be a validated surrogate for hepatic iron concentration. The sponsor stated that the estimated time of the NDA submission would be July, 2002.

- July 12, 2002. Teleconference. The sponsor indicated that it would be submitting data from its own trial (LA-12, treatment of hemosiderosis with either deferoxamine or deferiprone) and published literature to support its application for approval. The Division stated that published literature could be used to support the data from the adequate and well-controlled trial. The Division asked for data on thalassemia patients not treated with either deferoxamine or deferiprone.
- September 4, 2003. Denial of request for Fast Track designation due to the availability of a safe and effective alternative (i.e., deferoxamine).
- November 3, 2003. Teleconference. Sponsor believed that Fast Track designation should be approved. The Division indicated that Fast Track could be reconsidered if the sponsor proposed the use of deferiprone in patients unable to receive deferoxamine or could provide a program that sought to demonstrate improved effects of deferiprone on serious outcomes.
- January 26, 2004. Fast track status granted for deferiprone based on potential for safe and effective use in patients who are unable to be treated with deferoxamine.
- July 9, 2004. Pre-NDA meeting. Discussion of required pre-clinical studies that needed to be performed. The sponsor indicated that it planned to perform a meta-analysis of all of its trials to support its application for approval. The Division indicated that adequate and well-controlled studies were required to support an application for approval. The sponsor stated that it planned to submit multiple studies (not adequate or well-controlled) in support of its application as well. The sponsor indicated that it would also seek approval for the use of deferiprone in diseases in which hemosiderosis occurred (sickle cell anemia, myelodysplastic syndrome) for which studies were likely to be insufficient to establish efficacy and/or safety. The sponsor indicated that no study had been performed with deferiprone that specifically targeted the pediatric population.
- December 14, 2004. Meeting to discuss the primary endpoint. The sponsor had completed a number of clinical trials (LA-01, LA-16, LA-12, LA-03) whose primary endpoint was a measurement of tissue iron, usually hepatic. The sponsor requested that the primary endpoint for its various trials would be changed to "sequential serum ferritin

measurements". The Division indicated that this change would not be appropriate. The sponsor indicated that it would be submitting its NDA in 2005.

- May 15, 2006. Pre-NDA meeting. In response to the sponsor's questions, the Division provided the following clinical responses:

- Question 1. Does the FDA agree that the collective clinical data on the efficacy of deferiprone are appropriate and sufficient for an evaluation of the clinical efficacy of deferiprone?

**FDA response. The four controlled trials (LA-01, LA08-9701, LA12-9907, and LA16-0102) that are submitted as the pivotal trials to support the indication requested may not be sufficient.**

- All studies included only patients with  $\beta$ -thalassemia
  - The prospective studies (LA-01, LA08-9701, and LA16-0102) were all small (35, 30, and 29 patients receiving deferiprone, respectively). Study LA12-9907 was a retrospective trial.
  - The use of changes in serum ferritin and in MRI T2\* as measures of efficacy are not well established. There should be evidence presented that they are not merely surrogate endpoints, but indicate clinical benefits on morbidity and/or mortality in patients with iron overload.
  - The determination of clinical efficacy is a review issue.
  - At the meeting, please briefly discuss the extent of GCP compliance and availability of source clinical data for inspection verification of LA-01, LA08-9701, LA16-0102.
- Question 2. Does the FDA agree that the evidence of beneficial effect on cardiac morbidity and survival, supported by the efficacy endpoints of cardiac magnetic resonance imaging, serum ferritin levels and liver iron concentrations, are acceptable approaches for approval?

**FDA Response. Theoretically, these approaches could be acceptable.**

**However, the following points should be considered:**

- The purported beneficial effect on cardiac morbidity and mortality is based on a retrospective, non-randomized trial (Borgna-Pignatti).
- The summarized data do not provide validation of an increase in cardiac MRI T2\* as a surrogate of a clinically meaningful endpoint for the efficacy of deferiprone.
- The statistical differences noted in the supporting studies may not be clinically significant.
- Changes in serum ferritin levels are difficult to interpret because serum ferritin is subject to variations induced by a number of mechanisms that are unrelated to total body iron stores.
- Change in LIC using liver biopsy has generally been considered to be the standard measure of efficacy in response to iron chelation therapy, and only a fraction of patients in your trials had assessments of LIC by biopsy.

- Question 3. For the Borgna-Pignatti et al. epidemiology study (2005), does the FDA agree that the submission of the literature publication, statistical report, and data listings will be sufficient for the evaluation of efficacy?  
**FDA Response: You can submit the information. However, these data cannot be used to establish or support efficacy. If you submit the information, you will need to submit the protocol and all protocol amendments. All of the data collected in the study should be submitted to the NDA.**
  
- Question 4. Does the FDA agree that the collective clinical data on the safety of deferiprone are appropriate and sufficient for evaluation of the safety of deferiprone?  
**FDA Response: No. All data on all postmarketing reports of adverse events should be submitted to the NDA. In addition, all reports of serious adverse events associated with the administration of deferiprone up to the completion of the review of the NDA should be submitted to the Division. In regard to patients with neutropenia or agranulocytosis, a case report form should be submitted for each patient.**
  
- Question 6. Ferriprox is being developed for the treatment of iron overload in patients with excessive body iron stores due to chronic transfusion therapy. Does the FDA agree with the proposed indication statement?  
**FDA Response: No. The submitted data include studies performed in patients with  $\beta$ -thalassemia almost exclusively. The indication, if approved, will reflect the population enrolled in the trials.**
  
- Question 10. According to the Guidance document Providing Regulatory Submissions in Electronic Format–NDAs, dated January 1999, the need for patient profiles depends on the indication; they may not be needed at all or may be needed only for patients who discontinued or had a serious adverse event (SAE). Please confirm whether patient profiles should be included in the submission, and if so, for what patients.  
**FDA Response. Patient profiles should be submitted for all patients in any of the trials who died, suffered a serious AE, discontinued study drug because of an AE or were discontinued from any trial for any reason. Case report forms should be submitted for all deaths, AEs, and any withdrawal from the study because of AEs. All discontinuations should be presented fully and the reason for discontinuation explained.**

**Additional FDA comments**

### **General Considerations**

- **Some of the studies terminated earlier than expected. Provide an explanation for those terminations.**
- **All Foreign postmarketing experience data should be submitted in the NDA.**
- **Provide a clear presentation of the efficacy and safety of deferiprone based on comparisons to control groups (including historical controls where concurrent controls are not available).**
- **We are concerned that your database may not satisfy the regulatory requirements for “adequate and well controlled” trials. Additionally, data from retrospective studies are generally not adequate for approval of a drug.**
- **The statistical analysis plans for the various trials are not clearly delineated. Comparative trials between deferiprone and deferoxamine should be either superiority or non-inferiority in design. If a non-inferiority design is selected, the effect size of the standard therapy must be well established in order to determine the delta margin. The effect size of deferoxamine is not well characterized. A preliminary review of the comparative studies submitted indicates that deferiprone is not superior to deferoxamine in reducing serum ferritin. It is not possible to assess the non-inferiority of deferiprone compared to deferoxamine from the data and analyses provided.**
- **Since many of the patients in the target population are of pediatric age, it is advisable to analyze subsets of the pediatric population for efficacy and safety.**
- **The variability of protocol specified endpoints for the different studies will complicate the review for determining the efficacy of deferiprone.**

### **Additional meeting discussions**

*ApoPharma addressed FDA’s question regarding early termination of studies during discussion of Questions 1 and 2 stating that LA-01 was terminated early partially due to investigator non-compliance. ApoPharma added that the decision to terminate LA-01 was a difficult one for all involved parties.*

*FDA noted ApoPharma may have enough information to support the filing of a marketing application for Ferriprox. ApoPharma reminded FDA that there are data available from prospective, randomized trials that the FDA has not seen. ApoPharma requested guidance from the FDA regarding what is needed and how it should be submitted. FDA instructed ApoPharma that the NDA should highlight the pivotal studies that ApoPharma is proposing (including any studies undergoing reanalyses) to support the marketing approval for deferiprone.*

*FDA expressed concern that, based on the discussion, significant amounts of information have not been submitted to the IND therefore, based on the limited data provided the NDA database did not appear to be typical. Again the FDA reiterated the need for ApoPharma to organize the NDA highlighting the pivotal studies that they were relying upon for marketing approval.*

***FDA indicated its understanding was that ApoPharma has proposed that the efficacy of the marketing application will be supported by Study LA16-0102 as an adequate and well controlled study in addition to supporting studies including the Borgna-Pignatti epidemiology study and LA12-9907. ApoPharma acknowledges that drawing support for the NDA from only one well-controlled study is not typical, but may be justified.***

*Reviewer Comments. The interactions between the Division and the sponsor often led to a divide between what the sponsor and the Division considered to be acceptable evidence for approvability. In particular, in the pre-NDA meeting dated May 15, 2006, the Division indicated that the sponsor's endpoint measurement (change in T2\*) was not a valid endpoint for the determination of the efficacy of the use of deferiprone. Apparently, by the time of that meeting, the sponsor had already completed the trial. In various meetings, the sponsor stated that the drug was already approved in a number of countries, that it had been in study/use in humans for almost 20 years, that there was a significant enthusiasm for its approval by physicians and patients, and that it believed that the studies that it had performed and the literature available about the drug were sufficient for the Agency to approve the drug. The Division was not inclined to accept these lines of reasoning.*

## **2.6 Other Relevant Background Information**

Deferiprone was first approved for human use in the European Union in 1999, and is currently approved in 59 countries including countries in Asia, Africa and the Middle East. The indication in the EU is "Ferriprox is indicated for the treatment of iron overload in patients with thalassaemia major when deferoxamine therapy is contraindicated or inadequate." In its assessment of the data from clinical trials of deferiprone and in recommending the approval of the drug, the Committee for Proprietary Medicinal Products stated that Marketing Authorization should be granted under "exceptional circumstances" because of the fact that "in the present state of scientific knowledge, comprehensive information on the safety and efficacy of the medicinal product cannot be provided".

(b) (4)

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## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

The data for Study LA 16-0102, the single adequate and well controlled trial submitted by the sponsor appear to be adequate in quality and integrity. The data for Study 12-9907, a supportive study submitted by the sponsor, were not generated by the sponsor but were obtained from a registry that had been established at a single institution to measure the natural history of thalassemia. These data were made available to the sponsor, but case report forms were not available. Data from some of the earlier studies of the use of deferiprone, particularly Studies LA 01 and LA 03 are incomplete, and their quality and integrity are suspect because of disagreements that arose between the investigator and the sponsor. Consultation with the Division of Scientific Investigation has been requested, in particular regarding Studies LA 16-0102, LA 01 and LA 03.

### **3.2 Compliance with Good Clinical Practices**

The sponsor has stated that the clinical trials that form the basis of the application (Studies LA 16-0102 and 12-9907) were conducted in accordance with the provisions of Good Clinical Practices.

### **3.3 Financial Disclosures**

The sponsor has filed Form FDA 3454 indicating that it has not entered into any financial arrangement with any of the clinical investigators involved in the various clinical trials whereby the value of compensation would be affected by the outcome of the trial.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

## **4.1 Chemistry Manufacturing and Controls**

The original CMC submission was received on March 12, 2007 and there were 4 amendments made with the last recorded on December 21, 2007. The final recommendation was that the NDA was approvable with respect to CMC information.

## **4.2 Clinical Microbiology**

There have been no submissions of Clinical Microbiology for deferiprone.

## **4.3 Preclinical Pharmacology/Toxicology**

The original Pharmacology/Toxicology submission was received at the FDA on December 22, 2006 and the review was completed by David Bailey on June 27, 2007. Based on the review, it was recommended that additional non-clinical studies should include an electrophysiology study in hErg cells; lifetime carcinogenicity studies; and a fertility and early embryonic development study. In response, the sponsor submitted a submission dated March 19, 2008 whose review was completed on August 4, 2008. The responses were adequate except that the sponsor stated that the fertility/embryonic study would be performed after approval. The Division indicated that the latter study would have to be completed prior to approval.

## **4.4 Clinical Pharmacology**

The original Clinical Pharmacology submission was submitted on September 26, 2007, and the review was completed on March 27, 2008. Deficiencies included a lack of: pharmacokinetic/pharmacodynamic (PK/PD) studies in persons with hepatic or renal dysfunction; PK studies in persons exposed to the 33 mg/kg/d dose under chronic dosing conditions; dose proportionality studies; drug interaction studies; QC information; individual PK results; QTc studies; effect of age on PK results; and, method of dose selection from a dose response standpoint.

### **4.4.1 Mechanism of Action**

Deferiprone is a bidentate iron chelator that preferentially binds trivalent iron cations ( $\text{Fe}^{3+}$ ) in a 3:1 (deferiprone:iron) complex which is then excreted into the urine.

### **4.4.2 Pharmacodynamics**

In a study of nine iron overloaded subjects receiving deferiprone at a dose of 75 mg/kg/d, mean urinary iron excretion was  $22.5 \pm 8.0$  mg/day. A dose deferiprone of 75 mg/kg/d caused a negative iron balance equivalent to an oral dose of deferasirox of 40 mg/kg/d or to a parenteral dose of deferoxamine of 40 mg/kg/d. Most of the iron excreted after deferiprone administration is excreted in the urine.

### 4.4.3 Pharmacokinetics

Deferiprone is rapidly absorbed from the gastrointestinal tract and shows little binding to plasma proteins. Both deferiprone and its 1:3 ligand:iron complex are uncharged at physiological pH. Most of the ingested drug is excreted in the urine as the pharmacologically inactive glucuronide and the remainder as unchanged deferiprone or the chelation complex. The elimination half-life is 2-3 hours. Deferiprone is relatively lipophilic and is able to permeate cell membranes and possibly chelate intracellular iron.

## 5 Sources of Clinical Data

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### 5.1 Tables of Studies/Clinical Trials

Type of study	Study identifier/ Study Title	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s), Dosage regimen; Route of administration	No. of subjects	Health subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Efficacy	LA16-0102: Randomized trial comparing the relative efficacy of deferiprone to that of deferoxamine in removing excess cardiac iron in thalassemia major patients	Module 5.3.5.1.1	Primary objective: To determine if Ferriprox® (deferiprone) exhibits superior efficacy in removing excess iron from the heart compared to Desferal® (deferoxamine), as reflected by MRI T2* assessments  Secondary objective: To evaluate relative efficacy of Ferriprox® with respect to Desferal® as assessed by serum ferritin concentration and LIC	Multicenter, randomized, open-label, active controlled clinical trial	Test product: Ferriprox® 500 mg film-coated tablets <ul style="list-style-type: none"> <li>25 mg/kg, p.o., t.i.d., first 4 weeks.</li> <li>28.3 mg/kg, p.o., t.i.d., subsequent 4 weeks.</li> <li>33.3 mg/kg, p.o., t.i.d., remaining of the trial.</li> </ul> Comparator product: Desferal® <ul style="list-style-type: none"> <li>50 mg/kg/day, s.c., up to 12 hours infusion, 5-7 days/week</li> </ul>	61 dosed; 56 completed	<ul style="list-style-type: none"> <li>Thalassemia major</li> <li>Ongoing chelation therapy with Desferal® for at least the past 5 years</li> <li>Not exposed to Ferriprox® within the last 2 years if the patients have been exposed to Ferriprox® for ≤ 6 months</li> <li>Abnormal heart MRI T2* ≥ 8 ms and &lt; 220 ms</li> </ul>	12 months	Completed; Full
Efficacy	LA12-9907: Retrospective assessment of heart failure and survival during iron chelation with deferiprone or deferoxamine in subjects with transfusion-dependent β-thalassemia	Module 5.3.5.1.2	Primary objective: Investigate incidence of cardiac disease and survival in patients treated with Ferriprox® compared to patients treated with deferoxamine  Secondary objective: Evaluate progression of cardiac disease in patients treated with either Ferriprox® or deferoxamine	Open label, controlled, single center, parallel, longitudinal, retrospective assessment	Test product: Ferriprox® 500 mg film-coated tablets <ul style="list-style-type: none"> <li>75 mg/kg/day, p.o., 7 days/week</li> <li>The dose was adjusted to patient need within range from 35-100 mg/kg/day</li> </ul> Comparator product: Deferoxamine <ul style="list-style-type: none"> <li>20 to 60 mg/kg/day, s.c., 8-12 hours infusion, 4-7 days/week</li> </ul>	168 screened; 129 completed	<ul style="list-style-type: none"> <li>Transfusion-dependent β-thalassemia</li> <li>Treated for at least four years with Ferriprox® (deferiprone) or deferoxamine</li> </ul>	5 years	Completed; Full
Efficacy and Safety	LA08-9701: Safety and efficacy of alternating deferoxamine and deferiprone compared to deferoxamine alone in the treatment of iron overload in thalassemia patients	Module 5.3.5.1.3	Evaluate relative efficacy and safety of alternating use of Ferriprox® and Desferal® in comparison with current standard monotherapy, Desferal®	Randomized, open label, controlled, parallel clinical trial	Test product: Ferriprox® 500 mg film-coated tablets <ul style="list-style-type: none"> <li>25 mg/kg, p.o., t.i.d., 5 days/week</li> </ul> Desferal® for the combination arm <ul style="list-style-type: none"> <li>20-60 mg/kg/day, s.c., 8-12 hours infusion, 2 days/week</li> </ul> Comparator product: Desferal® <ul style="list-style-type: none"> <li>20-60 mg/kg/day, s.c., 8-10 hour infusion, 5-7 days/week</li> </ul>	59 dosed; 59 completed	<ul style="list-style-type: none"> <li>Transfusion-dependent thalassemia receiving chelation therapy with deferoxamine</li> <li>Serum ferritin concentration between 1000 and 4000 µg/L</li> </ul>	12 months	Completed; Full

Type of study	Study identifier/ Study Title	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s), Dosage regimen; Route of administration	No. of subjects	Health subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Safety	LA10-9902: Population monitoring cytogenetics study. An open label, single crossover design study to determine the clastogenic potential of deferiprone (L1) and compare that to the clastogenic potential of Desferal® (deferoxamine) in iron-overloaded, transfusion dependent individuals with thalassemia	Module 5.3.5.1.4	To determine if there is significant change in the frequency of chromosomal aberrations in circulating lymphocytes in subjects receiving deferoxamine therapy following a switch to deferiprone; and to compare that frequency in subjects that switched from deferiprone to deferoxamine  To determine the frequency of chromosomal aberrations in circulating lymphocytes in subjects following long term therapy with deferiprone compared to long term deferoxamine therapy.	Single center, open label, single treatment, active controlled, crossover design with no intervening drug-free period	Test product: Deferiprone (1 <sup>st</sup> transfusion cycle) • 25 mg/kg, p.o., t.i.d., a period of at least 20 days Deferoxamine (evening of the 2 <sup>nd</sup> transfusion cycle) • 20-60 mg/kg/day, s.c., 4-7 days/week, until day 20 of the transfusion cycle  Comparator product: Deferoxamine (1 <sup>st</sup> transfusion cycle) • 20-60 mg/kg/day, s.c., 4-7 days/week, a period of at least 20 days Deferiprone (evening of the 2 <sup>nd</sup> transfusion cycle) • 25 mg/kg, p.o., t.i.d., until day 20 of the transfusion cycle	20 dosed; 20 completed	<ul style="list-style-type: none"> <li>Patients with thalassemia major, who are regularly transfused with blood filtered by a blood bank, for white blood cells,</li> <li>Receiving ongoing chelation therapy with deferoxamine or deferiprone for the past three months</li> </ul>	A period of at least 20 days	Completed; Full
Efficacy and Safety	LA-02: Trial of deferiprone in thalassemia	Module 5.3.5.2.1	Primary objective: To determine incidence of agranulocytosis and other serious adverse events  Secondary objective: To determine the efficacy of deferiprone in treatment of iron-overload, as assessed by serum ferritin concentration	Prospective, multi-centered, open label, single treatment, uncontrolled clinical study	Test product: Deferiprone, 500 mg film-coated tablets • 25 mg/kg, p.o., t.i.d.	187 dosed; 162 completed	<ul style="list-style-type: none"> <li>Patients 10 years or older with transfusion dependent <math>\beta</math>-thalassemia</li> <li>Serum ferritin level above 2000 <math>\mu</math>g/L or a liver iron above 4.0 mg iron/g dry weight liver</li> <li>Unable or unwilling to take deferoxamine</li> </ul>	12 months	Completed; Full

Type of study	Study identifier/ Study Title	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s), Dosage regimen; Route of administration	No. of subjects	Health subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Efficacy and Safety	LA-02/06: Clinical study report for 4 years of therapy with Ferriprox™ in patients participating in studies LA-02/06	Module 5.3.5.2.2	LA-02: Primary objective: to determine incidence of agranulocytosis and other serious adverse events  Secondary objective: to determine the efficacy of deferiprone in treatment of iron-overload, as assessed by serum ferritin concentration  LA-06: Primary objective: to monitor long-term safety and effectiveness of Ferriprox® in the same cohort of patients as LA-02	Multi-centered, open-label, uncontrolled maintenance study	Test product: Ferriprox® 500 mg film-coated tablets • 25 mg/kg, p.o., t.i.d.	LA-02 : 187 dosed; 162 completed;  LA-06: 160 dosed; 84 completed	<ul style="list-style-type: none"> <li>LA-02: • Patients 10 years or older with transfusion dependent <math>\beta</math>-thalassemia</li> <li>• Serum ferritin level above 2000 <math>\mu</math>g/L or a liver iron above 4.0 mg iron/g dry weight liver</li> <li>• Unable or unwilling to take deferoxamine</li> <li>LA-06: • Patients who have completed LA-02 and are willing to continue treatment with Ferriprox®</li> </ul>	1 year under LA-02 and 3 years under LA-06 for a total of 4 years	Completed; 4-year report

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Type of study	Study identifier/ Study Title	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s), Dosage regimen; Route of administration	No. of subjects	Health subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Efficacy and Safety	LA-02/06: Clinical study report for 7 years of therapy with Ferriprox™ in patients participating in studies LA-02/06	Module 5.3.5.2.3	<p><b>LA-02:</b>                      Primary objective: to determine incidence of agranulocytosis and other serious adverse events</p> <p>Secondary objective: to determine efficacy of deferiprone in treatment of iron-overload, as assessed by serum ferritin concentration</p> <p><b>LA-06:</b>                      Primary objective: to assess the occurrence of adverse events and long-term effectiveness of deferiprone in the same cohort of patients as LA-02</p> <p>Secondary objective: To provide study medication to patients until licensure of product or cessation of clinical development</p>	Multi-centered, open-label, single treatment, uncontrolled maintenance study	Test product Ferriprox® 500 mg film-coated tablets <ul style="list-style-type: none"> <li>• 25 mg/kg, p.o., t.i.d.</li> </ul>	LA-02 : 187 dosed; 162 completed  LA-06 (48 month interim Statistical Report): 160 dosed; 84 completed  LA-06 (7 year Statistical Report): 160 dosed; 57 completed	LA-02 <ul style="list-style-type: none"> <li>• Patients 10 years or older with transfusion dependent <math>\beta</math>-thalassaemia</li> <li>• Serum ferritin level above 2000 <math>\mu</math>g/L or a liver iron above 4.0 mg iron/g dry weight liver</li> <li>• Unable or unwilling to take deferoxamine</li> </ul> LA-06 <ul style="list-style-type: none"> <li>• Patients who have completed LA-02 and are willing to continue treatment with Ferriprox®</li> </ul>	7 years	Completed; 7-year report

Type of study	Study identifier/ Study Title	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s), Dosage regimen; Route of administration	No. of subjects	Health subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Efficacy and Safety	LA-01: Randomized trial of deferiprone (L1, Ferriprox™) and deferoxamine (DFO) in thalassaemia major	Module 5.3.5.4.1	<ol style="list-style-type: none"> <li>1. Comparison of the relative effectiveness of deferiprone and deferoxamine as reflected by the ability of each chelator to:                             <ol style="list-style-type: none"> <li>a. achieve net negative iron balance</li> <li>b. reduce tissue stores of iron</li> <li>c. reduce body stores of iron</li> </ol> </li> <li>2. Comparison of the compliance with deferiprone and deferoxamine</li> <li>3. Testing of relative safety of deferiprone and deferoxamine</li> <li>4. Comparison of the relative quality of life enjoyed by patients during administration of either chelator</li> </ol>	Multi-centered, open-label, randomized, parallel active-controlled study	Test product: Deferiprone, 500 mg film coated tablets <ul style="list-style-type: none"> <li>• 25 mg/kg, p.o., t.i.d.</li> </ul> Comparator product: Deferoxamine <ul style="list-style-type: none"> <li>• 50 mg/kg, s.c., up to 12 hours infusion, 4-7 times/week</li> </ul>	71 dosed <ul style="list-style-type: none"> <li>• 35 in deferiprone</li> <li>• 36 in deferoxamine</li> </ul> 42 completed <ul style="list-style-type: none"> <li>• 21 in deferiprone</li> <li>• 21 in deferoxamine</li> </ul>	<ul style="list-style-type: none"> <li>• Patients 6 years and 10 months of age or older with <math>\beta</math>-thalassaemia</li> </ul>	2 years followed by a 1 year follow-up period	Completed; Full

Type of study	Study identifier/ Study Title	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s), Dosage regimen; Route of administration	No. of subjects	Health subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Efficacy and Safety	LA-03: The long term efficacy and safety of deferiprone in patients with transfusion-dependent thalassaemia (formerly compassionate use of deferiprone in thalassaemia patients)	Module 5.3.5.4.2	Under compassionate use program: to collect clinical experience with the use of deferiprone therapy for the treatment of iron overload.  Long-term primary objectives: to determine the long-term safety and efficacy of deferiprone	Single centre, open label study	Test product: Deferiprone <ul style="list-style-type: none"> <li>• Until OCT 1993, the test product was manufactured at University of Toronto and encapsulated by Novopharm Inc., Canada.</li> <li>• No data regarding quality of this product is available to ApoPharma Inc.</li> <li>• 25 mg/kg, p.o., t.i.d.</li> </ul> Deferiprone, 100 mg, 250 mg and 500 mg film-coated tablets <ul style="list-style-type: none"> <li>• From OCT 1993, the test product was manufactured by Apotex Inc.</li> <li>• 25 mg/kg, p.o., t.i.d.</li> </ul>	29 patients enrolled.  25 dosed with Apotex formulation.  No data were available for other 4 patients	<ul style="list-style-type: none"> <li>• Patients 10 years of age or older</li> <li>• Transfusion-dependent thalassaemia patients with iron overload</li> <li>• Unable to take currently available chelation therapy</li> <li>• Or had a history of serious non-compliance with currently licensed iron chelation therapy.</li> </ul>	4 years (University of Toronto formulation)  3 years (Apotex Inc. formulation)	Completed; Full

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Type of study	Study identifier/ Study Title	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s), Dosage regimen; Route of administration	No. of subjects	Health subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Efficacy and Safety	LA-04/06B: The compassionate use of deferiprone (L1) in patients with thalassemia	Module 5.3.5.4.3	Primary objective: to provide treatment of chronic iron overload in patients with transfusion dependent anemia for whom deferoxamine is contraindicated or inadequate  Secondary objective: to assess long-term safety and efficacy of Ferriprox® alone or in combination with deferoxamine for the treatment of chronic iron overload in patients with transfusion dependent anemia	Compassionate Use Program under LA-04 protocol.  Ferriprox® was supplied in 3-month allotments for an approved patient until licensure of the product or until the patient is withdrawn from the program.	Test product: Ferriprox® 500 mg film-coated tablets • 25-33 mg/kg, p.o., t.i.d.	86 dosed as of 28 FEB 2006	<ul style="list-style-type: none"> <li>Patients with thalassemia</li> <li>Patients with other chronic iron-overload conditions</li> <li>Require iron chelation</li> <li>Deferoxamine is contraindicated or inadequate (unwilling, unable, allergy, toxicity, lack of effect, inability to comply with parenteral infusions, or unavailability of the drug).</li> </ul>	Mean duration for all patients (N=86): • 1.3 (0-9.8) years  Mean duration for thalassemia patients (N=58): • 1.2 (0-8.4) years  Mean duration for patients with other chronic transfusion-dependent conditions (N=28): • 1.3 (0-9.8) years	Ongoing; Interim report
Efficacy and Safety	LA-11: Prevention of iron mediated oxidation of RBC and platelet membranes in $\beta$ -thalassemia diseases by deferiprone (L1)	Module 5.3.5.4.4	To determine the efficacy of Ferriprox® for reducing the iron overload in Thai patients with $\beta$ -thalassemia/ hemoglobin E diseases  To determine the safety of Ferriprox® for the treatment of iron overload in Thai patients.	Prospective, open label, uncontrolled study	Test product: Ferriprox® • Mean dose 48.1 $\pm$ 5.74 mg/kg, p.o., b.i.d. or t.i.d.	24 dosed; 15 completed	Thai patients with $\beta$ -thalassemia/ hemoglobin E disease	Mean time on therapy: • 334 $\pm$ 179 (5-526) days  16 patients were treated for more than 1 year  20 patients were treated for longer than 3 months	Completed; Full
Efficacy and Safety	LA-15-0002: Safety and efficacy of Ferriprox® for the treatment of iron overload in subjects with transfusion-dependent thalassemia in Iran	Module 5.3.5.4.5	Primary objective: To monitor the efficacy and safety of Ferriprox® for treatment of iron overload in subjects with transfusion dependent thalassemia in Iran	Single center, open label, single treatment, uncontrolled study.	Test product: Ferriprox® • 25 mg/kg, p.o., t.i.d.	29 dosed; 26 completed	<ul style="list-style-type: none"> <li>Subjects with transfusion-dependent <math>\beta</math>-thalassemia</li> <li>Last serum ferritin value, assessed within the past 12 months, was found to be greater than 2500 mg/L.</li> </ul>	3 months	Completed; Full

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Type of study	Study identifier/ Study Title	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s), Dosage regimen; Route of administration	No. of subjects	Health subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Efficacy	Borgna-Pignatti et al. (Blood 2006): Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia	Module 5.3.5.4.6	To compare the occurrence of cardiac disease and survival in patients treated only with deferoxamine (DFO) and in patients who had their therapy switched from DFO to deferiprone (DFP) during the study period.	Epidemiologic, observational study.	Test product: Deferiprone • 75 mg/kg/day, p.o., in 3 divided doses  Comparator product: Deferoxamine • 50 mg/kg/day, s.c., 5-6 times/week	359 patients treated with deferoxamine only  157 patients switched to deferiprone at one point during the study period	<ul style="list-style-type: none"> <li>Patients with thalassemia major</li> <li>Born between 1970 and 1993</li> <li>As of Jan 1995, were alive, had not had a cardiac event, received chelation therapy throughout study period and on follow-up, had not undergone bone marrow transplant</li> </ul>	9 years	Completed; Publication and Statistical Report
Efficacy and Safety	LA17-9701: The safety and effectiveness of deferiprone in a large-scale, 3-year study in Italian patients.	Module 5.4	To evaluate the long-term safety and efficacy of deferiprone	Open label, uncontrolled, active drug surveillance	Test product: Deferiprone • 75 mg/kg/day, p.o., in 3 divided doses	532 dosed  Treatment with deferiprone: • < 1 year, 13 patients • 1 to 2 years, 63 patients • 2 to 3 years, 167 patients • At least 3 years, 168 patients	<ul style="list-style-type: none"> <li>Thalassemia major or intermediate</li> <li>Serum ferritin &gt; 2000 µg/L or liver LIC &gt; 4 mg/g liver dry weight</li> </ul>	Mean 2.27 years	Completed; publication.

MRI = Magnetic Resonance Imaging  
 LIC = Liver iron concentration  
 ALT = Alanine aminotransferase  
 p.o. = oral  
 s.c. = subcutaneous  
 t.i.d. = three times a day  
 b.i.d. = twice a day

## 5.2 Review Strategy

The sponsor submitted a single study (LA 16-0102) as its pivotal trial and provided a second study (LA 12-9907) as a supportive study. In addition, the sponsor submitted other trials that it had performed (see Table above). These were reviewed and are commented upon, but are judged not to be adequate and well-controlled trials. The sponsor also submitted a number of published papers that it believes support the efficacy and safety of the use of deferiprone.

This review focuses primarily on Study LA 16-0102 because it is the only study that the sponsor indicates is an adequate and well-controlled trial of the use of deferiprone for the stated indication. The other submissions were reviewed and comments for these are included.

## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 Study LA 16-0102 (Submitted as the lone pivotal trial)

The first patient was enrolled in this trial on January 14, 2003 and the last patient was completed on October 13, 2004. Four sites were engaged in the trial: 2 sites in Athens, Greece; 1 site in Cagliari, Italy; and 1 site in Torino, Italy. The final study report was available on December 12, 2005. Two committees were established to oversee the study. These included a Steering

Committee that provided scientific direction, and a Safety Monitoring Committee that insured the safety of study subjects.

### **5.3.1.1 Objectives**

The primary objective of the study was to determine whether orally administered deferiprone exhibited superior efficacy in removing excess iron from the heart compared to the efficacy of standard subcutaneous infusions of deferoxamine, as reflected by MRI T2\* assessments of the heart in subjects treated with either chelator.

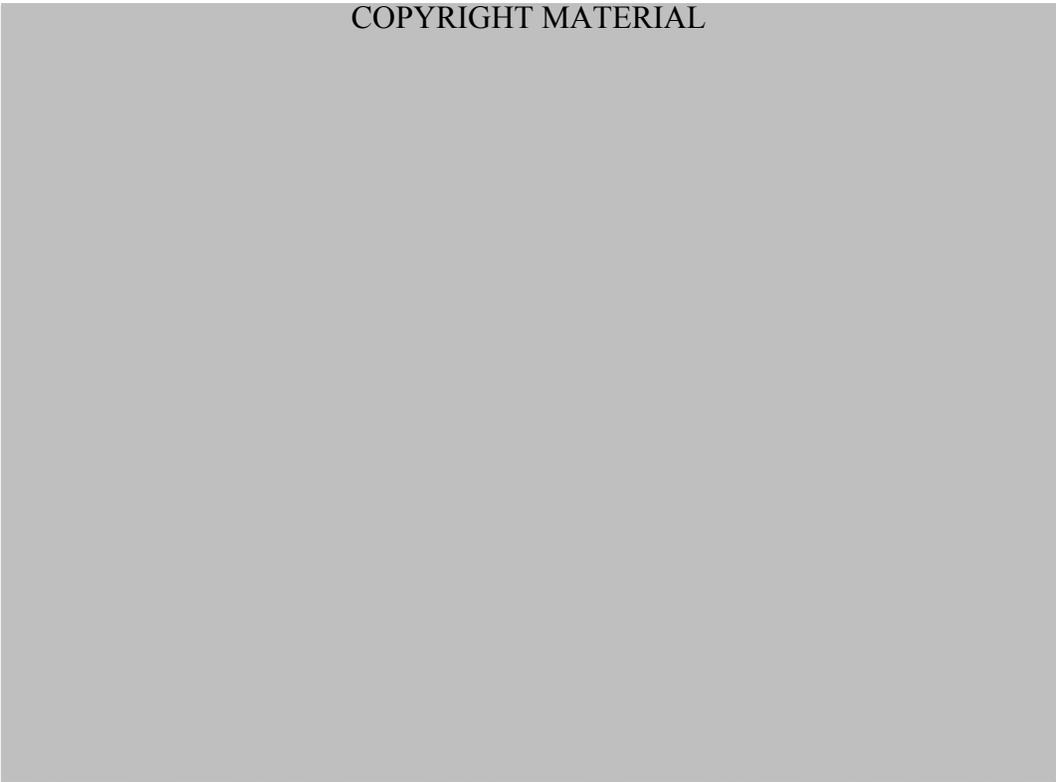
The secondary objective was to evaluate the relative efficacy of deferiprone with respect to that of deferoxamine as assessed by serum ferritin concentration and the liver iron concentration (LIC). LIC was assessed by the use of a superconducting quantum interference device (SQUID) BioSusceptometer.

*Reviewer Comments. The primary objective of the study would be appropriate if the sponsor had assessed the clinical benefit of each of the two drugs on the prevention or treatment of heart disease because heart failure due to iron overload of the heart is the leading cause of morbidity and mortality in thalassemia patients who receive multiple transfusions. Instead, the sponsor has selected a method of measurement that is of uncertain clinical significance as discussed below. The secondary objectives are those that have heretofore been employed in most studies of the efficacy of the use of iron chelators for transfusion-related hemosiderosis.*

*The methods of measurement employed in the trial are of concern for the following reasons:*

- The sponsor has not provided data to assure that MRI T2\* as a measurement of iron in the heart is actually correlated with the quantitation of iron content of the heart. Correlation studies have only been performed in gerbils. The sponsor has submitted a single case report in a human of the relationship of MRI T2\* with post-mortem chemical iron quantitation of the heart. In response to a request for information from the Division dated May 19, 2009, the sponsor submitted the following graph based on data developed by Dr. Dudley Pennell that shows the correlation between the “ex-vivo” MRI T2\* and the cardiac dry weight iron content (determined by inductively coupled plasma atomic emission spectrometry performed by Dr. Tim St. Pierre, Perth, Australia) in a total of 7 hearts examined after death. The data are unpublished but were presented by Dr. Pennell at a meeting with the Division on April 13, 2009. Dr. Pennell indicated that the data points represent multiple samples from the hearts, each assessed with both MRI and spectrometry. The data points for T2\* greater than 30 ms were all from a single heart. A paper with the data has been submitted for publication.*

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**Figure 2-1 Slide illustrating the curvilinear relationship between T2\* and chemically measured iron concentrations in the heart. Presented by Dr. Pennell at the meeting with the FDA on 13 Apr 2009.**

- The sponsor has not provided prospective data that demonstrate what degree of change in MRI T2\* measurement of iron in the heart might be considered clinically meaningful*

*as an appropriate surrogate for morbidity and/or mortality in patients with transfusion-related hemosiderosis.*

- *Serum ferritin levels may not be an appropriate surrogate for mortality and/or morbidity in patients with transfusion-related hemosiderosis. The literature suggests that patients with consistent serum ferritin levels below 2500 µg/L fare better than those with consistent serum ferritin levels above that level, but there does not appear to be a graded relationship between serum ferritin and clinical outcomes.*
- *Serum ferritin levels are influenced by factors other than the total iron present in the body.*
- *The correlation between serum ferritin levels and LIC measured by biopsy is approximately 0.62.*
- *The generally accepted standard for LIC is the chemical determination of iron concentration on liver biopsy. SQUID Biosusceptometry is known not to accurately measure LIC demonstrated by biopsy. Generally, there is a 1:2 ratio of iron concentration between SQUID:biopsy results. SQUID may be useful in the assessment of changes in LIC.*

### **5.3.1.2 Design**

The study was a multicenter (four sites), randomized, open-label, active-control trial. Eligible subjects were stratified according to their baseline cardiac MRI T2\* measurement ( $\geq 8$  to  $< 14$  milliseconds (ms) and  $\geq 14$  to  $< 20$  milliseconds) into Groups A and B, respectively. Subjects from each group were randomized equally between the 2 arms of the treatment. Group A subjects were to receive oral deferiprone and Group B subjects were to receive subcutaneously administered deferoxamine at doses indicated below. The treatment period was one year.

Patients enrolled in the trial were specifically required to refrain from the use of a long list of drugs which had the potential of causing hematological aberrations.

Subjects enrolled in the study were selected from the thalassemia major population who were currently receiving regular chelation with deferoxamine at the investigational sites. Randomization was performed by a statistician at ApoPharma.

This was an open-label study. However, the MRI T2\* cardiac status data were sent electronically for a blinded analysis by the MRI consultant (Dudley Pennell) at the Cardiovascular MRI unit of the Royal Brompton Hospital, London, United Kingdom.

Two amendments were made to the study after its commencement as follows:

- February 18, 2003. This amendment (#1) changed the randomization of subjects from “in blocks of two” to “participants from each group will then be randomized to either treatment”; eliminated scratch cards in favor of sealed envelopes as the means of informing patients and investigators as to assigned treatment arm; increased the allowed

age at enrollment from 30 to 36 years; changed scheduling of events to correspond to visits required for medical care; added a CMR derived LVEF at 6 months; and indicated that all MRI T2\* were to be forwarded electronically to Dudley Pennell at Royal Brompton Hospital.

- April 7, 2003. This amendment (#2) added a new investigational site; allowed for variability in the number of enrollees per site; and changed a criterion for entry for a well-transfused person from “a pre-transfusion Hb no less than 9 g/dL” to “a mean pre-transfusion Hb no less than 9 g/dL”.

*Reviewer Comments. An open-label study was performed because it would have been difficult to require patients receiving oral therapy with deferiprone to be treated with infusional placebo. Since the patients were previously receiving deferoxamine and had to have a diminished MRI T2\*, the patients selected may have been considered to be “failures” on deferoxamine and, by definition, not a representative sample of all patients with thalassemia.*

*The amendments did not appear to have a material effect on the interpretation of the study.*

*In response to a request for information from the Division, the sponsor offered the following:*

- *There was no formal Image Review Charter, but the procedures employed in the study were indicated in the sponsor’s response. The description of the procedures is at variance with the “Guidance for Industry: Developing Medical Imaging Drug and Biological Products. Part 3: Design, Analysis, and Interpretation of Clinical Studies” in a number of areas including: Random sequencing of images; Independent readings by more than one observer; Repeat readings by the same observer; Assessment of inter-reader and intra-reader variability; and, Inadequate de-identification. These deficiencies may have had an impact on the validity of the results.*

### **5.3.1.3 Patients**

Enrolled subjects had the following inclusion criteria:

- Diagnosis of thalassemia major with transfusion dependency
- Maintenance of a mean pre-transfusion hemoglobin (Hgb) of  $\geq 9$  g/dL
- Age between 18 and 36 years
- Receipt of deferoxamine for at least the last 5 years. If subject had previously received deferiprone, he/she must not have received it for at least the previous 2 years
- MRI T2\*  $\geq 8$  milliseconds and  $< 20$  milliseconds
- Use of adequate contraception and not breastfeeding
- Written informed consent

Enrolled subjects could not have the following exclusion criteria:

- Anemia other than thalassemia
- HIV positive

- Evidence of cardiomyopathy as demonstrated by a diminished left ventricular ejection fraction (LVEF) or a diminished left ventricular shortening fraction (LVSF)
- Presence of a significant arrhythmia or treatment for same
- Previous discontinuation of deferoxamine or deferiprone because of an adverse reaction to either chelator
- Abnormal liver function tests (>3x ULN)
- Disorders associated with neutropenia or thrombocytopenia in the previous 12 months
- Use of other investigational products
- Presence of medical conditions that make it unwise to enter the trial
- Pregnancy or breastfeeding
- Metallic objects in the body
- History of malignancy

Subjects were permitted to withdraw at any time without cause. The investigators or the sponsor could discontinue any patient from the trial and the reason for withdrawal would have to be provided. Patients had to be withdrawn for the following reasons:

- Administration of the wrong investigational agent
- Drug compliance of less than 70%
- Not meeting the inclusion/exclusion criteria
- Inability to tolerate the drug
- Severe or unexpected adverse reaction
- Upon 30 days of drug interruption
- Upon 4 consecutive missed visits
- Moderate or severe neutropenia ( $ANC < 1.0 \times 10^9/L$ )
- Thrombocytopenia (platelets  $< 50 \times 10^9/L$ )
- Pregnancy
- Noncompliance with weekly blood counts
- Seroconversion to HIV positive

*Reviewer Comments. The trial was restricted to patients with thalassemia major. The results may not be applicable to other populations. A large proportion of patients with myelodysplastic syndrome would be excluded on the basis of hematological values alone. The inclusion criteria do not mention any of the standard assessments for body iron stores (serum ferritin, LIC). The age range is compressed and does not include any pediatric patients. All patients with any evidence of heart disease are excluded. Therefore, the results can be extrapolated only to a very small segment of the possible targeted treatment population.*

#### **5.3.1.4 Drugs**

Patients randomized to Arm A were to receive oral deferiprone at a dose of 33.3 mg/kg three times daily (total daily dose of 100 mg/kg). Therapy was to be initiated at a dose of 75 mg/kg/d

in three divided doses with a minimal interval of 4 hours between doses. At week 4, the daily dose was to be escalated to 85 mg/kg/d; then, at week 8, the dose was to be escalated to 100 mg/kg/d. Lower doses could be prescribed in the event of the development of adverse reactions. The sponsor selected the 100 mg/kg/d dose because it is the maximum recommended dose where deferiprone has been approved. In the published literature, doses ranging from 25 to 150 mg/kg/d have been reported. The sponsor has not performed any formal dose-response studies.

Patients randomized to Arm B were to receive subcutaneous infusions of deferoxamine at a dose of 50 mg/kg/d for 5 to 7 days a week. A lower dose could be prescribed in the event of the development of adverse reactions. The dose used is the maximal recommended dose of the drug.

Deferiprone was manufactured by Apotex as 500 mg film-coated tablets. Deferoxamine was manufactured by Novartis and was available as 500 mg and 2 gram vials of sterile lyophilized deferoxamine mesylate.

The drugs were to be administered for a period of one year. Dose adjustments were made for changes in weight during the course of the trial.

[Note. The comparator selected was the only then-available iron chelator. Since the trial was completed, another iron chelator (deferasirox) has been approved for the treatment of transfusion-related hemosiderosis.]

*Reviewer Comments. The dose of deferiprone used in this trial was atypical. For most of the other studies performed by the sponsor, the usual total daily dose was 75 mg/kg/d.*

### 5.3.1.5 Efficacy

The primary efficacy measure was the subjects' cardiac iron status as determined by cardiac MRI T2\* assessment. MRI T2\* was measured at baseline, at 6 months and at 12 months (or at the time of early withdrawal). All cardiac iron concentration determinations were to be made 1 week after the appropriate corresponding transfusion visit. MRIs were performed either in Athens, Greece or Cagliari, Italy. Data from the 2 centers were transmitted electronically to Dudley Pennell at the Cardiovascular MRI unit of the Royal Brompton Hospital, London, United Kingdom for blind readings.

The secondary efficacy measurements were the assessment of serum ferritin concentration and LIC. Serum ferritin concentration was measured by microparticle enzyme immunoassay (MEIA) at baseline, quarterly and at end of treatment. The tests were performed at [REDACTED] (b) (4) using a validated kit supplied by [REDACTED] (b) (4). LIC was measured by SQUID at baseline and at 12 months. All SQUID measurements were performed in a single location in [REDACTED] (b) (4).

Cardiac function (left ventricular ejection fraction, LVEF) was also evaluated by CMR (at baseline, 6 months and 12 months) and echocardiography (LVEF and left ventricular shortening fraction, LVSF) (at baseline and at 12 months).

A quality of life (QOL) assessment using the RAND-36 questionnaire was performed.

No measurements of drug concentration were performed.

*Reviewer Comments. The sponsor makes the following statements regarding CMR:*

- *CMR is established in clinical practice for the diagnosis and management of diseases of the cardiovascular system, is accurate, reproducible and well validated, and provides an assessment of left ventricular volumes and ejection fractions.*
- *CMR has linked left ventricular systolic and diastolic dysfunction in beta thalassemia major with the absolute measurement of myocardial T2\*.*
- *CMR T2\* allows the diagnosis and treatment of iron-induced heart disease before overt cardiomyopathy develops.*
- *Liver T2\* measurements have shown a curvi-linear, inverse correlation between liver T2\* and LIC by liver biopsy.*

*I have reviewed the literature provided by the sponsor in support of the statements made above and have the following comments:*

- *CMR appears to be able to provide an assessment of left ventricular volumes and ejection fractions, but its correlation with LVEF obtained by echocardiography is imperfect because the latter method has a lower accuracy.*
- *The reference provided for the sponsor's assertion in Bullet #2, above, (Oliveri NF et al NEJM 1994; 331:574-578) was a study of the effects of deferoxamine therapy on morbidity and mortality in patients with thalassemia. The article indicates that patients with thalassemia have better outcomes when their serum ferritin is consistently <2500 µg/L compared to serum levels consistently in excess of that number. Nowhere in the article can I find any data on "the linking of ventricular function and myocardial T2\*". In addition, I believe that the article was published prior to any significant studies that measured T2\*, all of which commenced in the 21<sup>st</sup> century.*
- *CMR T2\* values below 10 ms appear to be associated with a greater frequency of the development of cardiac failure within one year compared to patients with CMR T2\* values above 10 ms.*
- *It appears that liver T2\* measurements have a curvi-linear inverse relationship with LIC as obtained by biopsy.*

*In clinical practice, measurements of serum ferritin and LIC have been the generally accepted methods of evaluation of the efficacy of therapy in persons with iron overload.*

*Acceptance of the sponsor's method of measuring the endpoint is dependent upon several assumptions, some of may not be true.*

- *First, I accept that excess iron in the heart is detrimental to cardiac function.*

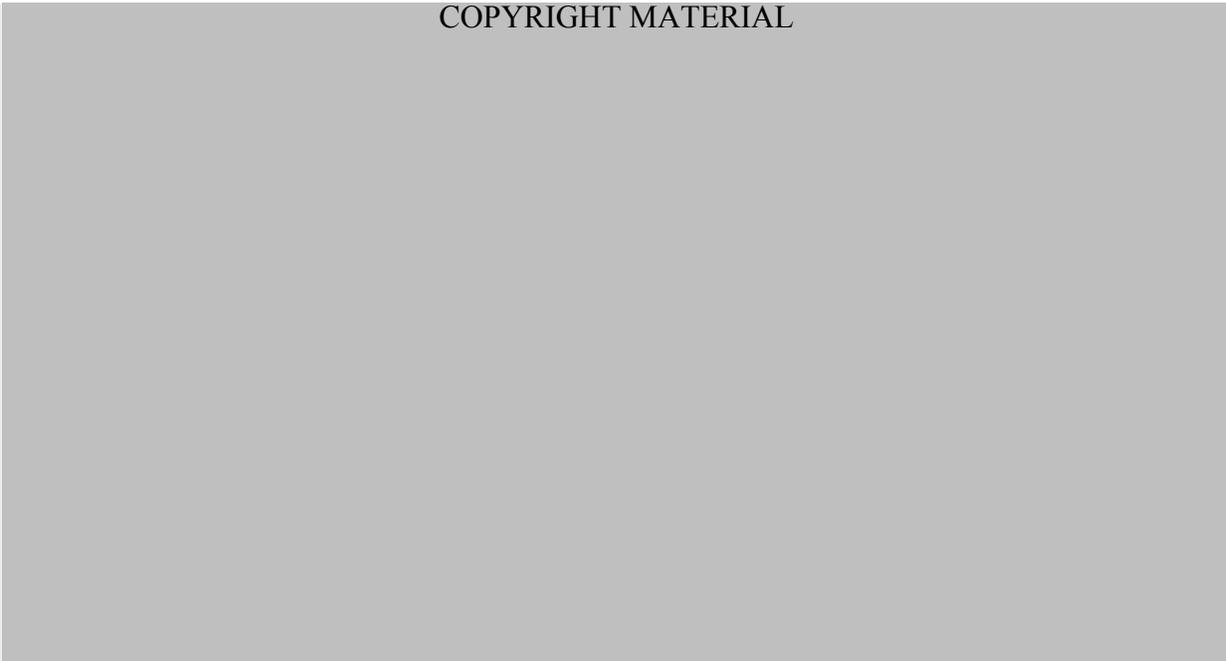
- *Second, I have some reservations of the ability of the MRI T2\* to accurately measure true iron concentration. The data presented by Dr. Pennell were performed in “ex vivo” hearts, rather than on MRI T2\* performed during life shortly before death and then spectrometrically measured for iron content after death. Importantly, the data presented by Dr. Pennell contain no information on the iron content of hearts with MRI T2\* measurements between 13.96 and 33.56 ms, and it is within these bounds that most persons with transfusion dependent thalassemia reside.*
- *Although it seems logical to conclude that an increase in MRI T2\* of the heart should be associated with improvement in function of the heart that would benefit both morbidity and mortality outcomes, there are no scientific data presented that support such a conclusion.*
- *The sponsor has not submitted any data as to the quantitative increase in the MRI T2\* that is required to indicate a clinical benefit in mortality or morbidity in iron overloaded thalassemia patients.*

*Therefore, I am not certain that I can accept MRI T2\* as even a surrogate endpoint.*

*In response to a request for information from the Division for the relationship between the MRI T2\* and measures of left ventricular function, the sponsor provided the following information:*

- *The relationship between MRI T2\* and LVEF and LVSF is a complex one, demonstrating a correlation only in conditions of iron overload, and becomes evident only at an MRI T2\* below 20 ms as shown in the following graph. Each data point represents the coincidental measurement of the MRI T2\* and the LVEF for a single patient. LVEF below 57% occur only in patients with a T2\* value of approximately 10 ms or below.*

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**Figure 1-1 Left ventricular ejection fraction vs. heart T2\*, from figure 3a in paper by Anderson et al.<sup>(1)</sup>**

- *In an analysis of the data from Study LA 16-0102, the sponsor states that there was a correlation between the MRI T2\* and the CMR-measured LVEF, but not with the echocardiography-measured LVEF or the LVSF (see Efficacy Results, below).*

### 5.3.1.6 Safety

Safety was assessed by evaluation of adverse reactions, including frequency, severity and causality, physical findings and by laboratory assessments. Because of previous observations, particular attention was directed to the assessment of hematological changes and changes in serum zinc levels. CBCs were required to be performed weekly.

Neutropenia was defined based on the level of the absolute neutrophil count (ANC) as follows:

- Mild. ANC between 1,000 and 1,500/mm<sup>3</sup>
- Moderate. ANC between 500 and 1,000/mm<sup>3</sup>
- Severe/Agranulocytosis. ANC below 500/mm<sup>3</sup>

Management guidelines for mild neutropenia included daily blood counts for 14 days. If the neutrophil count remained below 1,500/mm<sup>3</sup>, the deferiprone was to be discontinued, the patient was to be withdrawn from the study and followed until the count improved. Moderate neutropenia led to immediate discontinuation of deferiprone, withdrawal from the study and follow-up of blood counts until resolution. Rechallenge with deferiprone was not permitted.

Agranulocytosis led to immediate discontinuation of deferiprone, withdrawal from the study and follow-up of blood counts until resolution. In addition, a bone marrow examination was to be done, a sepsis evaluation was to be performed and the patient was to receive a granulocyte stimulating factor. Rechallenge with deferiprone was not permitted.

*Reviewer Comments. Neutropenia and agranulocytosis are well known adverse reactions associated with the administration of deferiprone, occurring in approximately 1% of treated subjects. The monitoring plan was acceptable.*

### **5.3.1.7 Statistics**

The statistical analysis plan (SAP) was dated October 24, 2004 and the statistical report was dated April 28, 2005.

For statistical evaluation of efficacy data, both the intent-to-treat (ITT) and the per protocol (PP) populations were evaluated. For statistical analysis of safety, the observed cases (OC) approach was to be used. The definitions are as follows:

- ITT population. This included all subjects who had received at least one dose of study drug and had at least a baseline and one post-baseline measurement. In the event of a missing observation for a subject, assessment would be based on the last observation carried forward (LOCF).
- PP population. This included all randomized subjects who had completed the trial. However, subjects withdrawn from the trial because they did not comply with the protocol were excluded from this population.
- OC population. Data from all randomized subjects were to be used for each visit. When no data were available at a particular visit, LOCF was not used to fill in missing data.

The primary efficacy analysis evaluated MRI T2\* data at baseline, and at 6 and 12 months after commencing treatment.

Secondary efficacy analyses evaluated serum ferritin levels at baseline and at 3 month intervals after commencing treatment; LVEF and LVSF at baseline and at 6 monthly intervals; and LIC by SQUID assessment at baseline and the end of the study.

Additional analyses included the effects of covariates (splenectomy, baseline serum ferritin level).

Safety analyses were performed for all adverse reactions, serious adverse reactions, serum alanine aminotransferase, absolute neutrophil count, serum zinc level, serum creatinine, hemoglobin and platelets.

Sixty (60) subjects were planned to be enrolled on the trial with an expected dropout rate of 20%. With the remaining subjects, it was believed that there would be an 80% power with an alpha

=0.025 (1-sided) to show that deferiprone demonstrated a greater increase in cardiac MRI T2\* from baseline after 1 year of therapy compared to deferoxamine, based on an expected difference of at least  $2.3 \pm 2.5$  ms between the 2 treatment groups, as determined in previous MRI T2\* data in patients with T2\* between 8 and 20 milliseconds.

In the original analysis plan, raw T2\* data values obtained to determine cardiac iron concentration were to be used for the primary statistical analyses. Because tissue iron is not linearly related to the inverse of the T2\*, this measure was changed by log-transformation prior to analysis to linearize the relationship and to provide an unbiased estimate of the relative change from baseline for both treatments. The 2-sample t-test was used to compare the mean changes in Log (MRI T2\*) from baseline to 6 and 12 months between the two treatment groups. ANOVA was to be used for the analysis of MRI T2\* data and other measures for cardiac functions.

Although not planned in the SAP, the effects of co-variates on MRI T2\* were investigated.

*Reviewer Comments. The statistical analysis plan is disconcerting for the following reasons:*

- *The SAP appears to post-date the completion of the trial rather than having been pre-specified in the protocol*
- *The sponsor states that data from previous studies were used to predict an expected difference of  $2.3 \pm 2.5$  ms in MRI T2\* between the 2 treated groups. However, the sponsor has not provided any evidence that a difference of  $2.3 \pm 2.5$  ms in T2\* measurement between the 2 treatment groups has any clinical relevance.*
- *The simple comparison between baseline and end of study LVEF and LVSF may provide a statistically significant difference but may not represent a clinically meaningful benefit. The sponsor has not provided evidence to support that an improvement in LVEF and LVSF in the range of this study indicates clinical benefit, particularly for patients with a normal LVEF and LVSF. In addition, there are multiple other determinants of LVEF and LVSF that would have to be controlled before an interpretation of change could be made.*
- *The studies referenced by the sponsor regarding the prognostic significance of measuring LVEF in congestive heart failure (CHF) were all performed using echocardiograph in patients who all had diminished values (usually markedly) and virtually all the patients described had coronary artery disease as the cause for their CHF. In addition, by definition, CHF is generally associated with a diminished LVEF. Little is known about the natural history of persons with varying degrees of iron overload of the heart and a normal LVEF.*
- *Consultation with the Division of Cardiological and Renal Drug Products indicates that it has not been their policy to approve drugs for the treatment of heart failure on the basis of data for LVEF or LVSF. Their criteria for efficacy include such clinical endpoints as death and the need for hospitalizations for congestive heart failure.*

*The review by the statistics division will be important.*

### 5.3.1.8 Ethics

The study was performed in accordance with the ethical principles of the Declaration of Helsinki 2000 or with the laws of the country in which the research was conducted, whichever provided greater subject protection, and in compliance with the principles of the ICH E6 Good Clinical Practices, ApoPharma standard operating procedures and local requirements. Written informed consent from the subjects was required. Approval of the protocol by the local IRB was required before subjects from each institution could be enrolled. Subjects had to provide written informed consent before enrollment in the study.

### 5.3.1.9 Results

5.3.1.9.1 Disposition of Patients. A total of 160 subjects were screened for inclusion/exclusion criteria and all were assessed for MRI T2\* and LVEF. Subjects were selected if the MRI T2\* was between 8 and 20 ms and the LVEF was >56%. Ninety-nine were excluded (some for several reasons) because:

- The MRI T2\* values were less than 8 ms (11%) or greater than 20 ms (76%)
- Decreased LVEF (2%)
- Abnormal liver enzymes (3%)
- Unsuitable psychological condition (1%)
- Age <18 or >30 years (8%)
- Claustrophobia (3%)
- Pre-transfusion Hgb <9 g/dL (3%)
- Refuse or unable to participate (7%)

A total of 61 patients enrolled in the trial at the 4 investigational sites. They were stratified into 2 groups based on baseline MRI T2\* (8 to 14 ms, 14 to 20 ms) and then randomized between Arms A and B. While equal numbers were randomized into the 2 arms for the lower MRI T2\* group (n=16 assigned to each treatment arm), there were a few more subjects (n=16) in the deferoxamine treated arm than in the deferiprone arm (n=13) in the higher T2\* group.

Fifty-six (56) subjects completed the study and 5 subjects discontinued prematurely, 2 in the deferiprone arm (1 because of elevated liver enzymes and 1 who developed cytomegalovirus hepatitis and did not wish to continue) and 3 in the deferoxamine arm (2 for personal reasons and 1 because of deteriorating heart function).

There were several minor protocol violations. Three (3) of the enrolled patients did not meet the inclusion criteria (Hgb of 8.3 g/dL at baseline; late signing of the informed consent form;

interruption of deferoxamine for 4 years and 10 months before enrollment). Four subjects had minor deviations in dosing of either deferiprone or deferoxamine usually for short periods of time during the year of treatment. There were some protocol deviations related to fact that some assessments were performed outside of the time window specified in the protocol.

*Reviewer Comments. The sponsor had to screen 160 subjects with transfusion dependent  $\beta$ -thalassemia who had been receiving deferoxamine for at least 5 years in order to obtain 61 eligible subjects. The most common cause for not qualifying for the trial (76% of rejections) was that the CMR T2\* exceeded 20 ms. This, according to the sponsor, indicates that there is no consequential excess iron in the heart suggesting that the use of deferoxamine was effective in these patients. Therefore, the patients who were enrolled in the trial should be considered to be “deferoxamine failures” and are, in essence, destined to be treated for an additional 12 months in the trial with a therapy that has already been demonstrated to be ineffective. This logic will have to be considered when the analyses of the results are reviewed.*

### 5.3.1.9.2 Demographic characteristics.

All subjects were Caucasians. The subjects in each arm were similar in gender, mean age, ethnicity and weight as shown in the following table.

Demographic Characteristics

Characteristics	Randomized Treatment Groups	
	Ferriprox [n=29]	Desferal [n=32]
<b>Gender</b>		
Male	15 (52%)	16 (50%)
Female	14 (48%)	16 (50%)
p-value <sup>†</sup>	1.000	
<b>Age (years)</b>		
Mean $\pm$ SD	25.1 $\pm$ 3.8	26.2 $\pm$ 4.7
Min, Max	18, 32	18, 35
p-value <sup>*</sup>	0.3335	
<b>Ethnicity</b>		
Greek	16 (55%)	18 (56%)
Italian	13 (45%)	14 (44%)
p-value <sup>†</sup>	1.000	
<b>Race</b>		
Caucasian	29 (100%)	32 (100%)
p-value <sup>†</sup>	N/A	
<b>Weight (kg)</b>		
Mean $\pm$ SD	57.7 $\pm$ 7.9	60.6 $\pm$ 13.2
Min, Max	43.8, 72.3	41.1, 91.0
p-value <sup>*</sup>	0.3018	

Sponsor Table, CSR, Page 6

The number of patients entered on the trial from each institution is shown in the following table.

Number of patients from each institution enrolled on protocol

Site Number	Investigators	Location	Number of Subjects Enrolled (Ferriprox / Desferal)
A1	Markissia Karagiorga-Lagana, M.D.	Aghia Sophia Children's Hospital Thivon & Livadias 11527 Athens, Greece	18 (8/10)
A2	Vasilis Ladis, M.D.	1 <sup>st</sup> Department of Pediatrics Athens University Aghia Sophia Hospital Thivon & Livadias 11527 Athens, Greece	16 (8/8)
C1	Renzo Galanello, M.D.	Dipartimento di Scienze Biomediche e Biotecnologie Università Degli Studi di Cagliari Ospedale Regionale Microcitemie, A.S.L. 8 Via Jenner S/N 09100 Cagliari, Italy	22 (10/12)
T1	Antonio Piga, M.D.	Università degli studi di Torino Dipartimento di Scienze Pediatriche e dell'Adolescenza Piazza Polonia, 94 101 26, Torino, Italy	5 (3/2)

Sponsor Table, CSR, Page 23

Fewer patients assigned to the deferiprone arm (14%) had had a splenectomy as compared to those in the desferal arm (34%), although the difference was not statistically significant. Infections with hepatitis B and C were equally distributed. This is shown in the following table.

Baseline Medical Conditions

Characteristics	Randomized Treatment Groups	
	Ferriprox [n=29]	Desferal [n=32]
<b>Splenectomy</b>		
Yes	4 (14%)	11 (34%)
No	25 (86%)	21 (66%)
p-value	0.0791	
<b>Hepatitis C</b>		
Positive	18 (62%)	16 (50%)
Negative	11 (38%)	16 (50%)
p-value	0.4408	
<b>HIV</b>		
Positive	0 (0%)	0 (0%)
Negative	29 (100%)	32 (100%)
p-value	Not applicable	

Sponsor Table, CSR, Page 64

Fewer patients assigned to the deferiprone arm had a baseline serum ferritin greater than 2500 µg/L (17%) compared to those assigned to the deferoxamine arm (41%).

Baseline Serum Ferritin Levels

Serum Ferritin	Randomized Treatment Groups		
	Ferriprox [n=29]	Desferal [n=32]	Total [n=61]
≤ 2,500 µg/L	24 (83%)	19 (59%)	43
> 2,500 µg/L	5 (17%)	13 (41%)	18
P-value	0.0546		

Sponsor Table, CSR, Page 65

Mean baseline serum ferritin levels were also lower in the deferiprone treated patients (1791 ± 1029 µg/L) compared to those in the deferoxamine treated patients (2795 ± 2441).

Concurrent medication use was universal and differed somewhat between the 2 arms of the trial, particularly with respect to medications for respiratory symptoms (deferiprone, 28%; deferoxamine, 69%). Statistical analyses were difficult to interpret because of the small number of patients in the trial.

Compliance with therapy was assessed by the number of openings (deferiprone) and the number of completed infusions (deferoxamine). The overall compliance with treatment was similar between the 2 arms (deferiprone, 93.7 ± 5.3%; deferoxamine, 93.2 ± 9.7%; p=0.8122).

*Reviewer Comments. Although this was a randomized trial, there are several differences in the demographic characterization of the populations in the 2 arms of the trial that are of concern. Most differences do not rise to a statistical level of significance, but this may be due to the small numbers of patients in the trial. Attention should be paid to the following:*

- *There was a large imbalance in the enrollment of subjects at these sites. Thirty-four (34) of the enrollees were from one institution (Aghia Sophia Hospital), 22 subjects were enrolled in Cagliari, and only 5 were enrolled at the institution in Torino.*
- *Enrollees in the deferoxamine arm were more likely to have demographics that could suggest a more impaired population including:*
  - *Older age, thereby likely to have received a larger lifetime iron load because of more transfusions*
  - *Greater frequency of splenectomy, suggesting more severe disease*
  - *Higher mean baseline serum ferritin and greater percent of persons with serum ferritin in excess of 2500 µg/L, suggesting a larger lifetime iron load and a poorer response to deferoxamine prior to enrollment on the trial (all subjects were previously being treated with deferoxamine)*

### 5.3.1.9.3 Primary Efficacy Analysis

The primary efficacy variable was the assessment of myocardial iron concentration measured by MRI T2\* over the time of the treatment period. Assessments were performed at baseline, and at 6 and 12 months following the commencement of treatment. Log-transformation of the MRI T2\* data was used to linearize scaling because a difference of 2 or 3 units at a high MRI T2\* (e.g., 20 ms) does not have the same significance as a difference of 2 or 3 units at a low MRI T2\* (e.g., 10 ms). The 2-sample t-test was used to compare the mean changes in Log (MRI T2\*) at the various time intervals.

One subject in the deferoxamine arm had a baseline MRI T2\* only and was excluded from the ITT population. The following table shows the results of log mean MRI T2\* comparisons at the described time intervals in the ITT population.

MRI T2\* Values at Baseline and at 6 and 12 Months of Therapy

MRI T2* (milliseconds)	Randomized Treatment Groups					
	Baseline		6 Months		12 Months	
	Ferriprox [n=29]	Desferal [n=32]	Ferriprox [n=29]	Desferal [n=31] <sup>†</sup>	Ferriprox [n=29]	Desferal [n=31] <sup>†</sup>
Geometric Mean (milliseconds) <sup>*</sup>	13.03	13.32	15.37	14.43	16.51	15.01
Coefficient of Variation (%) <sup>‡</sup>	32	30	38	37	38	39
Percentage of Baseline			118	109	127	113
Ratio of Means (%) <sup>§</sup>	98		109		112	
p-value <sup>  </sup>	0.7731		0.0404		0.0228	

Source: [Appendix 12.1.9 \(Statistical Report, Appendix 2.1.1\)](#)

\* Geometric mean is defined as antilog of the mean of the log data

† Subject C1-40 had baseline MRI T2\* level value only and was not eligible to be included in the ITT population.

‡ Coefficient of variation is defined as  $\sqrt{[e^{\text{variance}} - 1]}$ , where variance is the variance of the mean in log scale.

§ The ratio is defined as Ferriprox mean/Desferal mean. At 6 and 12 months, the ratio is corrected for the difference in baseline mean between the two treatment groups by dividing it by 0.98.

|| The Log (MRI T2\*) between the Ferriprox and Desferal treatment groups was compared by the two-sample t-test.

Sponsor Table, CSR, Page 69

A similar analysis of the PP population gave virtually identical results.

*Reviewer Comments. See my previous comments regarding this endpoint. I am not able to determine whether a change in MRI T2\* from 13.03 ms at baseline to 16.51 ms after 12 months of treatment, although perhaps statistically significant (at least as assessed by the sponsor's*

*methods), has any relationship to a clinically significant benefit, nor whether those results were superior to the change in MRI T2\* from 13.32 ms to 15.01 ms that was observed in the deferoxamine treated group. The sponsor has not provided documentation that links an increase in MRI T2\* to an improvement in clinical outcomes, nor information on the degree of increase in MRI T2\* that represents a quantitative improvement in cardiac iron concentration.*

**5.3.1.9.4 Secondary Efficacy Analyses.** There were a number of secondary efficacy analyses performed as follows.

- **CMR LVEF.** An analysis was performed on both the ITT and the PP population. One patient in the deferoxamine arm had only a baseline CMR LVEF and was therefore excluded from the ITT population. The baseline mean LVEF in the deferiprone arm was  $69.66 \pm 5.44\%$  and increased by  $3.07 \pm 3.58\%$  at 12 months after beginning treatment. The baseline mean LVEF in the deferoxamine arm was  $68.38 \pm 4.92\%$  and increased by  $0.32 \pm 3.38\%$  at 12 months after beginning treatment. The p value for the difference between the treatment groups was 0.0034. These data are shown in the following table.

CMR LVEF Values at Baseline and after 6 and 12 Months of Therapy

CMR LVEF (%)	Randomized Treatment Groups					
	Baseline		Change from Baseline to 6 Months		Change from Baseline to 12 Months	
	Ferriprox [n=29]	Desferal [n=32]	Ferriprox [n=29]	Desferal [n=31] <sup>†</sup>	Ferriprox [n=29]	Desferal [n=31] <sup>†</sup>
Mean $\pm$ SD	69.66 $\pm$ 5.44	68.38 $\pm$ 4.92	2.00 $\pm$ 2.73	0.52 $\pm$ 3.52	3.07 $\pm$ 3.58	0.32 $\pm$ 3.38
Min, Max	58, 80	60, 79	-3, 9	-9, 9	-3, 11	-8, 5
p-value*	0.3382		0.0744		0.0034	

Source: [Appendix 12.1.9 \(Statistical Report, Appendix 2.2.1\)](#)

CMF = cardiovascular magnetic resonance; ITT = intent-to-treat; LVEF = left ventricular ejection fraction; max = maximum; min = minimum.

\* Changes in CMR LVEF from baseline to 6 months and 12 months were compared between the two treatment groups by using the two-sample t-test.

<sup>†</sup> Subject C1-40 had baseline CMR LVEF level value only and was not eligible to be included in the ITT population.

Sponsor Table, CSR, Page 73

A similar analysis of the PP population gave virtually identical results.

No patient had an ejection fraction of less than 56% at any time during the study. The sponsor indicates that this implies that there was no evidence of congestive heart failure in any of the patients at any time (congestive heart failure is usually defined as an LVEF of <50%).

- Echocardiogram LVEF. An analysis was performed on both the ITT and the PP population. One patient in each arm had only a baseline ECHO LVEF and was therefore excluded from the ITT population. The mean baseline LVEF of subjects treated with deferiprone was  $64.69 \pm 6.72\%$  and over the course of 12 months of treatment, the LVEF increased by  $2.50 \pm 6.04\%$ . The mean baseline LVEF of subjects treated with deferoxamine was  $64.27 \pm 6.88\%$  and over the course of 12 months of treatment, the LVEF decreased by  $0.56 \pm 4.90\%$ . These data are shown in the following table.

Echocardiographic LVEF Values at Baseline and after 12 Months of Therapy

ECHO LVEF (%)	Randomized Treatment Groups			
	Baseline		Change from Baseline to 12 Months	
	Ferriprox [n=29]	Desferal [n=32]	Ferriprox [n=28 <sup>†</sup> ]	Desferal [n=31 <sup>†</sup> ]
Mean $\pm$ SD	64.69 $\pm$ 6.72	64.27 $\pm$ 6.88	2.50 $\pm$ 6.04	-0.56 $\pm$ 4.90
Min, Max	54, 79	50, 77	-9, 16	-8, 10
p-value	0.8088		0.0358	

Source: [Appendix 12.1.9 \(Statistical Report, Appendix 2.4.1\)](#)

ECHO = echocardiogram; ITT = intent-to-treat; LVEF = left ventricular ejection fraction; SD = Standard Deviation.

\* Mean changes from baseline to 12 months were compared between the two treatment groups by using the two-sample t-test.

<sup>†</sup> Subjects A1-47 and C1-40 did not have ECHO LVEF value at 12 months and were not eligible to be included in the ITT population.

Sponsor Table, CSR, Page 75

A similar analysis of the PP population gave virtually identical results.

- Echocardiogram LVSF. An analysis was performed on both the ITT and the PP population. One patient in each arm had only a baseline ECHO LVSF and was therefore excluded from the ITT population. The mean baseline LVSF of subjects treated with deferiprone was  $36.32 \pm 4.39\%$  and over the course of 12 months of treatment, the LVEF increased by  $2.62 \pm 7.41\%$ . The mean baseline LVSF of subjects treated with deferoxamine was  $36.38 \pm 4.25\%$  and over the course of 12 months of treatment, the LVSF decreased by  $1.08 \pm 3.82\%$ . These data are shown in the following table.

Echocardiographic LVSF Values at Baseline and after 12 Months of Therapy

ECHO LVSF (%)	Randomized Treatment Groups			
	Baseline		Change from Baseline to 12 Months	
	Ferriprox [n=29]	Desferal [n=32]	Ferriprox [n=28 <sup>†</sup> ]	Desferal [n=31 <sup>†</sup> ]
Mean ± SD	36.32 ± 4.39	36.38 ± 4.25	2.62 ± 7.41	-1.08 ± 3.82
Min, Max	31.2, 47.0	30.0, 44.0	-8.0, 12.0	-8.8, 8.0
p-value <sup>*</sup>	0.9540		0.0175	

Source: [Appendix 12.1.9 \(Statistical Report, Appendix 2.5.1\)](#)

ECHO = echocardiogram; ITT = intent-to-treat; LVSF= left ventricular shortening fraction; SD = Standard Deviation.

\* Mean changes from baseline to 12 months were compared between the two treatment groups by using the two-sample t-test.

† Subjects A1-47 and C1-40 did not have ECHO LVSF value at 12 months and were not eligible to be included in the ITT population.

Sponsor Table, CSR, Page 76

A similar analysis of the PP population gave virtually identical results.

*Reviewer Comments. In response to a request from the Division, the sponsor analyzed the correlations between the MRI T2\*, the CMR LVEF, the echocardiogram LVEF and the echocardiogram LVSF. There were statistically significant correlations (p value, 0.027, 0.0146) at 6 and 12 months of therapy, respectively, between the MRI T2\* and the MRI LVEF but not at baseline (p value, 0.2329). There were no statistically significant correlations between the MRI T2\* and the ECHO LVEF or the ECHO LVSF at baseline or at any follow-up evaluation, nor with the change in ECHO LVEF or the ECHO LVSF at the end of the study. The maximum correlation was 0.31. These data suggest that, at best, the change in MRI T2\* explains approximately 10% of the variation in heart function as measured by MRI LVEF, ECHO LVEF or ECHO LVSF.*

- Liver Iron Concentration (LIC). LIC was measured by SQUID. The mean baseline and end of treatment LIC are shown in the following table.

Liver Iron Concentration at Baseline and at End of Treatment

LIC (mg Fe/g dry weight liver)	Randomized Treatment Groups			
	Baseline		Change from Baseline to 12 Months	
	Ferriprox [n=28 <sup>†</sup> ]	Desferal [n=32]	Ferriprox [n=27 <sup>‡</sup> ]	Desferal [n=30 <sup>‡</sup> ]
Mean ± SD	6.16 ± 6.02	6.32 ± 5.77	-0.93 ± 2.93	-1.54 ± 2.49
Min, Max	1.5, 33.3	0.7, 26.4	-8.7, 5.2	-8.8, 1.6
p-value*	0.9161		0.3961	

Source: [Appendix 12.1.9 \(Statistical Report, Appendix 2.3.1\)](#)

Fe = iron; ITT = intent-to-treat; LIC = liver iron concentration; SD = Standard Deviation.

\* Mean changes from baseline to 12 months were compared between the two treatment groups by using the two-sample t test.

† Subject C1-44 did not have baseline LIC value only and was not eligible to be included in the ITT population.

‡ Subjects A1-20, C1-40, C1-44 and C1-52 did not have LIC value at 12 months and were not eligible to be included in the ITT population.

Sponsor Table, CSR, Page 78

Although there was no statistically significant difference in the mean LIC in the deferiprone treated subjects from baseline to end of study ( $-0.93 \pm 2.93$  mg Fe/g dry weight), there was a statistically significant difference from baseline to end of study in LIC ( $-1.54 \pm 2.49$  mg Fe/g dry weight,  $p = 0.0020$ ) in the deferoxamine treated subjects.

Similar analyses of the PP population gave similar results. Covariates (splenectomy status, hepatitis C status, baseline serum ferritin) had no significant influence on the comparison of LIC between the two treatment groups.

- Serum ferritin. The baseline mean serum ferritin level (1,790.6 µg/L) was lower in the deferiprone treated group compared to that in the deferoxamine treated group (2,795.1 µg/L). Mean serum ferritin levels tended to rise in the deferiprone treated patients at 3 months, but then there was a gradual fall until, at the end of study, the mean serum ferritin was 1,609.1 µg/L. In contrast, mean serum ferritin levels fell progressively in patients treated with deferoxamine, and plateaued at 12 months so that at the end of study, the mean level was 2.246.7 µg/L. These data are summarized in the following table.

Serum Ferritin Concentrations at Intervals of 3 Months

Serum Ferritin Concentration (µg/L)	Randomized Treatment Groups									
	Baseline		Change from Baseline to 3 Months		Change from Baseline to 6 Months		Change from Baseline to 9 Months		Change from Baseline to 12 Months	
	Ferriprox [n=29]	Desferal [n=32]	Ferriprox [n=29]	Desferal [n=32]	Ferriprox [n=29]	Desferal [n=32]	Ferriprox [n=29]	Desferal [n=32]	Ferriprox [n=29]	Desferal [n=32]
Mean ± SD	1790.6 ± 1028.9	2795.1 ± 2441.2	354.8 ± 743.3	-169.1 ± 814.4	150.9 ± 713.4	-314.3 ± 921.0	-72.3 ± 658.3	-548.4 ± 868.2	-181.0 ± 825.5	-466.1 ± 738.9
Min, Max	289, 5345	280, 9300	-394, 3610	-2222, 3041	-816, 1782	-3979, 1812	-1833, 1606	-2894, 306	-2179, 1990	-2208, 606
p-value*	0.0391		0.0113		0.0326		0.0199		0.1598	

Source: Appendix 12.1.9 (Statistical Report, Appendix 2.6.1)

SD = Standard Deviation.

\* Mean changes of serum ferritin concentrations from baseline to 3, 6, 9, and 12 months were compared between the two treatment groups by using the two-sample t-test.

Sponsor Table, CSR, Page 80

Similar analyses of the PP population gave similar results.

*Reviewer Comments. The measurements provided by the sponsor (LVEF, LVSF, serum ferritin, LIC) are often used clinically to evaluate cardiac function and to determine the effect of a drug on body iron levels. However, it is important to remember that these measurements may not be predictive of clinical benefit in altering morbidity or mortality in transfusion induced iron overload in patients with thalassemia. In addition, I have the following concerns about the measurements and their analyses:*

- *The LVEF and LVSF were normal throughout the trial in almost all patients. Small changes in these measurements that are all within the normal range may have no clinical significance.*
- *Consultation was requested from the Division of Cardiovascular and Renal Drug Products regarding the utility of measuring periodic LVEF and LVSF as a means of determining the clinical significance of a therapeutic intervention in persons with potential cardiac impairment. The response was provided by Drs. Shari Targum and Norman Stockbridge (see DFS, April 20, 2009). The following points were made:*
  - *The reviewer was unable to evaluate the clinical meaningfulness of small changes in ejection fraction or fractional shortening.*
  - *Meaningful clinical outcomes (e.g., heart failure, heart failure hospitalizations, mortality) should be used as the basis for a claim for reducing heart failure incidence.*
  - *Measurements of LVEF and LVSF are subject to inter-reader and intra-reader variability as well as reader expertise. It would be of interest to understand how these imaging studies were read.*
  - *LVEF and LVSF are measurements that can be influenced by loading conditions.*
  - *If the image readers were aware of the drug therapy in this open-label trial, then potential bias cannot be excluded.*

- *There is no validated correlation between serum ferritin as a continuous variable and morbidity or mortality in patients with transfusion dependent thalassemia. The correlation ( $r^2$ ) of serum ferritin with LIC measured by biopsy of the liver is approximately 0.62, and LIC by SQUID underestimates LIC by liver biopsy by a factor of approximately 2.*

### 5.3.1.9.5 Safety Evaluation

Safety was evaluated for all randomized patients (61 patients in total). Total exposure was 27 patient-years for the deferiprone treated patients and 30 patient-years for the deferoxamine treated patients. The mean dose of deferiprone was 92 mg/kg/d and the mean dose of deferoxamine was 43 mg/kg for 5.7 days/wk. Adverse reactions (AR) were summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) version 7.0. Fisher’s exact test was used to compare the incidence of each adverse reaction between the 2 treatment groups.

The most frequent adverse reactions are summarized in the following table.

Most Frequent Adverse Reactions reported in Study LA 16-0102

	Ferriprox Group		Desferal Group	
	Total Reports:	279	Total Reports:	131
	Total Subjects Reporting:	29	Total Subjects Reporting:	32
	Total Subjects:	29	Total Subjects:	32
	Total Exposure (subject-years):	27.34	Total Exposure (subject-years):	30.2
Body System	#	%	#	%
Preferred Term	Subjects		Subjects	
Gastrointestinal Disorders	19	65.52	6	18.75
General Disorders And Administration Site	3	10.34	11	34.38
Investigations	19	65.52	13	40.63
Metabolism And Nutrition Disorders	9	31.03	0	0.00
Musculoskeletal And Connective Tissue Disorders	12	41.38	7	21.88
Nervous System Disorders	8	27.59	6	18.75
Skin And Subcutaneous Tissue Disorders	3	10.34	6	18.75

Sponsor Table, CSR, Page 92, adapted

Gastrointestinal adverse reactions (AR) were more common in patients receiving deferiprone than in those receiving deferoxamine. Common symptoms included upper abdominal pain, nausea, vomiting, diarrhea and eructation. Administration site reactions (erythema, induration, inflammation and pruritus) occurred only in patients receiving deferoxamine. Hypersensitivity reactions were reported in 1 patient in each arm of the trial. The neutrophil count was decreased in 1 patient receiving deferiprone and in 4 patients receiving deferoxamine. No patients in either arm experienced agranulocytosis. Elevations in hepatic enzymes occurred in more patients in the deferiprone (alanine aminotransferase, 11 patients; aspartate aminotransferase, 6 patients; gamma-glutamyltransferase, 4 patients) compared to the deferoxamine treated patients (4; 1; and 0, respectively). There was also an upward trend in ALT at 3, 6 and 9 months in patients receiving deferiprone compared to those treated with deferoxamine, although the trend was no longer apparent at 12 months of treatment. T wave inversions occurred in 6 patients receiving deferiprone and none of those receiving deferoxamine. Other cardiac findings included ECG repolarization abnormality (3) and QT prolongation (1). More patients treated with deferiprone had an increase in appetite and weight gain than those treated with deferoxamine. Arthralgia was reported in 8 patients receiving deferiprone compared to 3 patients receiving deferoxamine.

Other adverse reactions were reported in approximately similar numbers of patients in each arm of the trial.

There were no deaths during the course of the trial.

There were 2 serious ARs in patients receiving deferiprone. One patient developed cytomegalovirus hepatitis (which led to drug discontinuation) and another experienced a corneal abscess. There were no serious ARs in the deferoxamine treated patients.

There were small decrements in serum zinc in patients treated with either medication. The clinical significance of this finding is not known. There were no clinically significant changes in serum creatinine or in measures of hematological values over the course of the trial.

The sponsor concludes that there were no new safety signals revealed in Study LA16-0102.

*Reviewer Comments. The safety database from this trial is inadequate because there were only 31 patients exposed to deferiprone during its conduct. From previous studies and postmarketing reports, gastrointestinal ARs, arthralgia and increases in serum transaminases are known to be associated with the use of deferiprone, and they occurred in this study as well.*

*Reviewer Comments regarding the Overall Efficacy and Safety Results of Study LA16-0102.*

*As noted, I do not think that there is meaningful evidence provided for either efficacy or safety of the use of deferiprone in patients with thalassemia and iron overload due to transfusion therapy in this study for the following reasons:*

- The numbers of patients in the trial were insufficient to provide robust evidence of either efficacy or safety.*
- The baseline demographics of patients in the two arms of the trial were not comparable.*
- The mean dose of deferiprone administered in the trial was 92 mg/kg/d, which is less than the maximally recommended dose proposed in the package insert.*
- The mean dose of deferoxamine administered in the trial was 43 mg/kg/d, which is less than the maximum commonly used dose of deferoxamine (50 mg/kg/d) and the planned dose for the trial. Therefore, some of the claimed beneficial comparative effects of deferiprone might have been due to suboptimal dosing with deferoxamine.*
- The primary endpoint analyzed in the trial (change in MRI T2\*) cannot yet be considered to be a clinically important benefit, nor is it established as a surrogate endpoint.*
- Analyses of the secondary endpoints do not add additional support for the efficacy of the use of deferiprone in these patients.*
- The sponsor may have demonstrated a statistically significant difference in the analyses of these endpoints (MRI T2\*, CMR LVEF, echocardiogram LVEF and LVSF), but there is no evidence that these differences in patients treated with deferiprone translate into a clinically meaningful benefit on either mortality or important morbidity.*
- The safety database from this study is entirely inadequate to establish that important toxicity has been properly defined and balanced against efficacy. The number of patients treated with deferiprone totaled only 29. In addition, the length of the study was only 12 months, and it would be expected that patients would be treated for a lifetime with deferiprone.*

### **5.3.2 Study LA 12-9907 (Submitted as a supportive study)**

This retrospective study was conducted to fulfill a specific obligation made by the sponsor to the Committee for Proprietary Medicinal Products (CPMP) of the European Medicine Evaluation Agency (EMA) at the time of the marketing authorization for deferiprone in the European Community (EC) in 1999. LA12-9907 sought to provide insight into the relative efficacy of deferiprone to that of deferoxamine on the prevalence or progression of cardiac disease and survival in patients with transfusion-dependent thalassemia.

#### **5.3.2.1 Objectives**

The primary objective of the study was to investigate the incidence of cardiac disease and survival in patients treated with deferiprone and to compare the results with those of patients treated with conventional therapy (daily subcutaneous infusion of deferoxamine) over the same period of time.

The secondary objective was to evaluate the progression of cardiac disease in patients participating in the study treated with either deferiprone or deferoxamine.

#### **5.3.2.2 Design**

This was a single center, retrospective analysis of medical records. All patients had a diagnosis of beta thalassemia and were followed at the Centro Microcitemie of the University of Turin, Italy, at which institution there has been a prospective survey on complications and survival in patients with thalassemia and transfusion related iron overload since 1981. Outcome measures included survival and the development or progression of heart disease observed after an interval that was variable but was at least 5 years in treatment duration. All patients were in a transfusion program that sought to maintain a mean hemoglobin level of 12 g/dL and a pre-transfusion level of 9.5 to 10.0 g/dL. Iron overload was assessed by quarterly serum ferritin levels and transfusional iron input. Some patients had LIC assessed by SQUID. Each patient had a periodic cardiac evaluation that included a complete medical history, echocardiography, ECG and ECG Holter monitoring. There was only one cardiologist who reviewed the cardiac data and he/she was said to be unaware of treatment assignment. Beginning in 1995, some of the patients at the center received deferiprone as either part of a clinical study (LA02, LA06, LA08) or on a compassionate use basis (LA17). The dose of deferiprone was 25 mg/kg three times daily. Other patients received deferoxamine at a dose of 20 to 60 mg/kg/d as an infusion of 8-12 hours 4 to 7 days a week. Patients treated with more intensive deferoxamine were evaluated separately.

It should be noted that no case report forms were prepared for any of the patients in the study, but that data were entered directly by the investigator into an electronic database and then provided to the sponsor.

### 5.3.2.3 Patients

All study patients had a diagnosis of transfusion-dependent beta thalassemia. Initially, the study intended to evaluate the clinical data of all patients whose medical history over 4 years was available to the investigator conducting the study. After the EMEA requested a longer follow up period, the study was amended to extend the period to 5 years. All patients treated at the center after December, 1995 were reviewed for entry into the study. Initially, the study was to be limited to those patients who had at least 3 serum ferritin determinations in the 2 years preceding the initiation of the study period. When it was determined that this would limit the number of otherwise qualified patients, this exclusion was eliminated. This decision was made after the completion of the review period and prior to the assessment of any data. To ensure compliance with the original protocol, a subgroup analysis (Subgroup I) limited to patients with at least 3 pre-study serum ferritin values was also performed and included in the report. A second subgroup (Subgroup II) analysis was done on 94 patients from either therapy arm that were matched for age at the start of chelation therapy to reduce the potential effect of age on the prevalence and/or progression of iron-induced cardiac disease.

Inclusion criteria were:

- Diagnosis confirmed by clinical and laboratory studies
- Age 5 years or older
- Receiving either deferoxamine or deferiprone

Exclusion criteria were:

- Patients with less than 3 serum ferritin results during the 2 years preceding the initiation of the study period (this criterion was subsequently removed)
- History of malignancy
- Disorder requiring radiation or chemotherapy
- HIV positive

### 5.3.2.4 Treatment

Deferiprone was provided as 500 mg scored, compressed film-coated tablets. The dose of deferiprone administered was 75 mg/kg/d (calculated to the nearest 250 mg) given orally in 3 divided doses. Because the dose was adjusted to the “degree of iron overload”, patients in this group actually received a range of doses from 35 to 100 mg/kg/d.

Control patients were treated with deferoxamine manufactured by Novartis Pharma from a range of 19 to 60 mg/kg given subcutaneously over 8 to 12 hours by pump 4 to 7 days per week.

Treatment compliance was evaluated by a retrospective analysis of monthly discussions between the doctor and the patient, the use of a Medication Event Monitoring System for deferiprone, and the record of the electronic infusor and pharmacy records for deferoxamine.

### 5.3.2.5 Efficacy and Safety Variables Assessed

The following parameters at the start of the study period were analyzed: gender; age; age at start of chelation therapy; transfusional iron input; mean of all serum ferritin levels in the 2 years preceding the review period; percentage of patients with more than 50% of serum ferritin results greater than 2500 µg/L; compliance with chelation therapy; percent of patients with hepatitis C antibodies; LIC in the year preceding the study, if available; urinary iron excretion in the year preceding the study; and, frequency of patients with cardiac disease at first cardiac assessment.

Data was collected from the first year following the start of the study to greater than 5 years.

The definition of cardiac disease included:

- New York Heart Association classification (none, I, II, III, IV)
- EF and SF parameters on echocardiography (EF considered abnormal if <55%, SF considered abnormal if <30%)
- Electrocardiographic /Holter monitor abnormalities

The primary efficacy endpoint was a composite of the occurrence of cardiac disease and survival based on the following:

- Frequency of patients with heart disease at last cardiac assessment
- Development of cardiac disease during the study in patients who were cardiac disease free at the outset of the study
- Heart disease free survival using the Kaplan Meier method

Additional endpoints evaluated included:

- Change in cardiac disease status based on changes in NYHA classification, shortening fraction and ejection fraction

The following were assessed during the conduct of the trial: compliance with chelation; duration of drug exposure; mean transfusional iron input; percent of patients with serum ferritin greater than 2500 µg/L in more than 50% of measurements; mean serum ferritin; LIC, when available; and, mean urinary iron excretion.

No formal safety data was collected for either arm in the study.

### 5.3.2.6 Statistics

Clinical records of 168 patients with beta thalassemia were screened and 129 met all the inclusion and exclusion criteria. Three analysis populations were defined:

- Main. 129 patients entered onto the trial (54 treated with deferiprone, 75 treated with deferoxamine)

- Subgroup I. 107 patients from the main group with at least 3 serum ferritin values during the 2 years prior to start of the study (50 treated with deferiprone, 57 treated with deferoxamine)
- Subgroup II. 94 patients from the main group matched for age at start of chelation therapy (47 patients treated with deferiprone, 47 treated with deferoxamine)

For analysis of change in cardiac disease status between the 2 therapy arms during the course of treatment, multiple parameters were analyzed by the Chi-square or the Fisher Exact tests. Heart disease free survival for patients who were disease free by NYHA criteria at the beginning of the review period was analyzed by the Kaplan-Meier method. The time of the development of heart disease was calculated as the time difference between the first available negative NYHA class and the first occurrence of NYHA class I or greater. ANOVA was used to determine differences between therapy groups over the years on shortening fraction and ejection fraction. The covariance structure used was compound symmetry and the method of determination was the Satterthwaite method. Two sample t-tests or Chi-square tests were used to compare baseline characteristics between the 2 treatment groups as well as to evaluate the differences related to chelation therapy during the study period for most of the variables listed above.

All statistical tests were 2-sided with a type I error of 0.05. In all 2-sample t-tests, when the test for equality of variances was significant ( $p < 0.05$ ), the test result based on unequal variances was used for determining the statistical significance of the comparison.

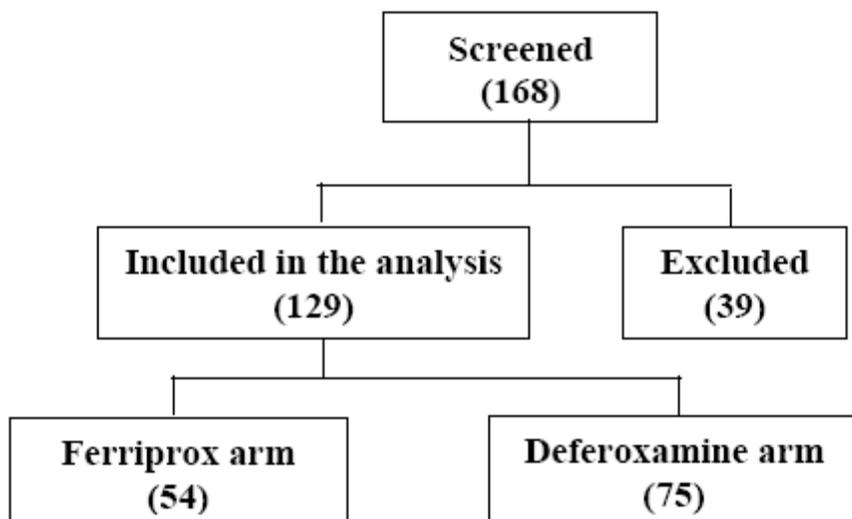
No formal determination of sample size was performed because of the retrospective design of the study.

The single change in the design of the study allowed the entry of patients who had had fewer than 3 serum ferritin determinations in the 2 years prior to the initiation of the study period, as noted above. However, two additional exclusion criteria were introduced after the data were collected and prior to the statistical analysis: patients with less than 4 years on either chelation therapy; or patients with less than 2 cardiac assessments.

### **5.3.2.7 Results**

#### 5.3.2.7.1 Disposition of Patients

The clinical records of 168 patients with beta thalassemia were screened and distributed according to the following scheme.



Of the 39 excluded patients, 16 did not have chelation therapy with one of the chelators for at least 4 years during the review period. Ten (10) patients were excluded because there was no information available for chelation therapy or cardiac assessments, and 6 patients were excluded because they had had only 1 cardiac assessment. One patient was excluded because he had antibodies against HIV. None of the excluded patients was diagnosed with a change in cardiac status or died during the review period. One patient who received deferiprone was maintained in the analysis group even though he had interrupted therapy for approximately 1 year during the review period.

Most of the patients treated on the deferiprone arm (46/54, 85.2%) were either unwilling to receive deferoxamine or had suffered an adverse reaction to the drug. Reasons for a switch from deferoxamine to deferiprone are shown in the following table.

**Table 9-1. Summary of reasons for switching from DFO to DFP therapy**

Switch to DFP Decode	n subjects	%DFP subjects
Unwilling to take DFO	32	59.3
Local reaction to DFO	7	13.0
Osteopenia	6	11.1
Allergic Reaction to DFO	3	5.6
Hearing loss	2	3.7
Allergic Reaction to DFO; sensory neural hypoacusis	1	1.9
Growth delay and bone disease	1	1.9
Osteoporosis	1	1.9
Unable to take DFO	1	1.9
<b>Total</b>	<b>54</b>	<b>100.0</b>

### 5.3.2.7.2 Efficacy Evaluation

Baseline characteristics of the 2 therapy groups are shown in the following table.

Patient demographics at the start of the study

	<b>Ferriprox<sup>®</sup></b> <b>N = 54</b>	<b>Deferoxamine</b> <b>N = 75</b>	<b>p-value</b>
Percentage of female	44% (24/54)	49% (37/75)	0.5832
Mean age ± SD [years]	17.1 ± 4.1	19.4 ± 6.9	0.0184
Mean age ± SD at the start of chelation therapy [years] (Number of patients available)	4.5 ± 2.7 (54)	6.8 ± 4.7 (72)	0.0010
Mean serum ferritin ± SD [µg/L] (Number of patients available)	2033 ± 919 (51)	1809 ± 1464 (60)	0.3277
Percentage of patients with more than 50% of their serum ferritin results > 2,500 µg/L	24% (12/51)	15% (9/60)	0.2529
Percentage of patients positive for HCV antibodies	87% (45/52)	80% (52/65)	0.3505
Mean transfusional iron input ± SD [mg Fe/kg body weight/day] (Number of patients available)	0.464 ± 0.085 (49)	0.432 ± 0.110 (61)	0.1024
Mean urinary iron excretion ± SD [mg Fe/day] (Number of patients available)	14.7 ± 10.7 (49)	15.5 ± 12.2 (48)	0.7292
Mean hepatic iron concentration ± SD - SQUID [mg Fe/g liver wet weight] (Number of patients available)	1.6 ± 0.7 (46)	0.9 ± 0.6 (16)	0.0023
Mean hepatic iron concentration ± SD - Biopsy [mg Fe/g liver dry weight] (Number of patients available)	8.5 ± 5.7 (34)	---	---
Percentage of patients with cardiac disease at the first assessment	13% (7/54)	16% (12/75)	0.6311

Sponsor table, CSR, page 40

Patients in the deferoxamine treated arm were older, had started chelation therapy at a later age and had lower SQUID measured LIC compared to patients in the deferiprone treated arm. There were no patients in the deferoxamine treated arm who had had LIC determined by liver biopsy. There were other differences present that did not reach statistical significance possibly because the number of entrants was small.

There was a significant difference between therapy groups for the proportion of patients with “cardiac disease” at last assessment (p=0.0280); for the development of “cardiac disease” among patients who were initially free of “cardiac disease” (p=0.0133); and, with worsening of NYHA classification from first to last assessment (p=0.0069) as shown in the following 3 tables.

Frequency of patients with cardiac disease at last assessment

Therapy	Yes (%)	No (%)	Total
Ferriprox <sup>®</sup>	7 (13.0)	47 (87.0)	54
Deferoxamine	22 (29.3)	53 (70.7)	75
Total	29	100	129

Sponsor table, CSR, page 43

*Reviewer Comments. There appears to be some discrepancy between the values listed in the table above and the data provided. In my review of Appendix 12.2.7 (Patient Listing of Cardiac Assessment Results), I found that there were 6 patients (#42, 48, 55, 67, 96 and 170) who were treated with deferiprone who were said to have cardiac disease at last assessment. There were 21 patients (#1, 8, 15, 16, 19, 20, 21, 22, 27, 30, 40, 44, 50, 61, 63, 76, 77, 101, 142, 154, and 171) who were treated with deferoxamine who were said to have heart disease at last assessment. I excluded patient #33 in the deferoxamine treated group, who I assume was included by the sponsor because that patient is classified as being NYHA I at month 72 without any apparent evidence for heart disease. Therefore, my analysis indicates that 6/54 (11.1%) of patients treated with deferiprone and 21/75 (28%) of patients treated with deferoxamine had evidence of cardiac disease at last assessment. These differences do not alter the interpretation of the results.*

Frequency of patients with cardiac disease during the study among patients initially free of cardiac disease

Therapy	Yes (%)	No (%)	Total
Ferriprox <sup>®</sup>	2 (4.3)	45 (95.7)	47
Deferoxamine	13 (20.6)	50 (79.4)	63
Total	15	95	110

Sponsor table, CSR, page 43

*Reviewer Comments. There appears to be some discrepancy between the values listed in the table above and the data provided. In my review of Appendix 12.2.7 (Patient Listing of Cardiac Assessment Results), I found that there were 3 patients (#48, 84 and 96), rather than 2, treated with deferiprone who were initially “cardiac disease free” and who developed “cardiac disease”. Two had a normal SF and EF and none had CHF at baseline. There were 11 patients (#20, 27, 40, 50, 61, 63, 76, 77, 122, 142 and 154), rather than 13, treated with deferoxamine who were initially “cardiac disease free” and who developed “cardiac disease”. I excluded the following deferoxamine treated patients (who I presume were counted by the sponsor):*

- *Patient #14. All studies performed on this patient were normal. A cryptic comment alongside the NYHA Class I listing states “Low variability of the heart frequency at the ECG Holter” although the Holter report states “No arrhythmia”.*
- *Patient #30. No data were available for this patient at baseline. This patient’s SF was 29 and EF was 42 at month 22 (these were his first listed measurements). Thereafter, his measurements were normal.*
- *Patient #33. This patient had normal studies throughout all periods, but was classified as NYHA I at 72 months for unknown reasons.*
- *Patient #101. This patient had only a Holter study that was normal at baseline. He had a SF of 25 at month 34. Thereafter, he had persistently low SF and EF.*

*Therefore, my analysis indicates that 3/47 (6.4%) of patients treated with deferiprone and 11/63 (17.5%) of patients treated with deferoxamine who were free of “cardiac disease” initially developed “cardiac disease” during the course of the study.*

Frequency of patients with a worsening of NYHA classification from first to last assessment

<b>Therapy</b>	<b>Yes (%)</b>	<b>No (%)</b>	<b>Total</b>
Ferriprox <sup>®</sup>	2 (3.7)	52 (96.3)	54
Deferoxamine	15 (20.0)	60 (80.0)	75
<b>Total</b>	<b>17</b>	<b>112</b>	<b>129</b>

Sponsor table, CSR, page 43

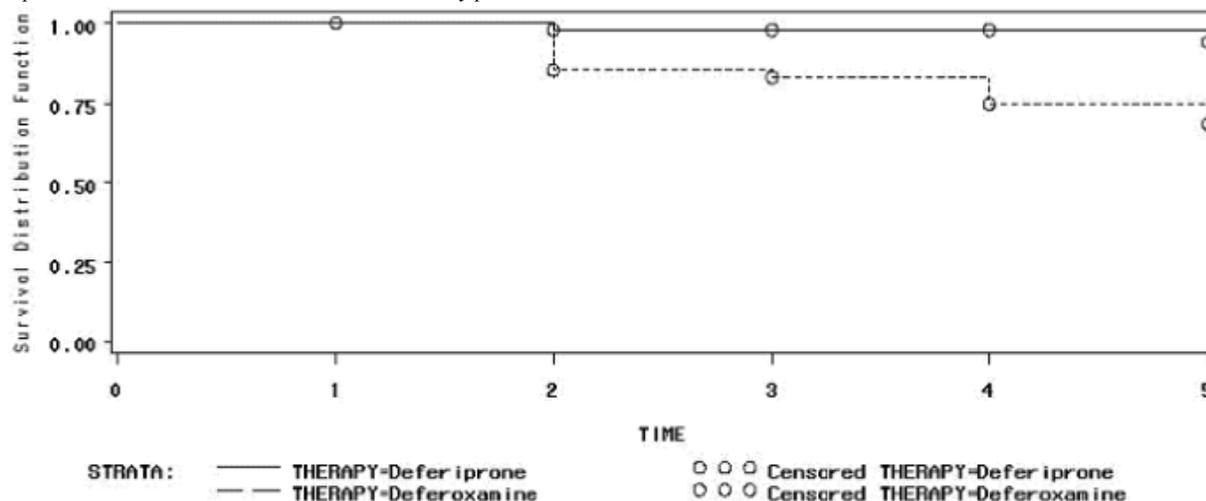
*Reviewer Comments. In my review of Appendix 12.2.7 (Patient Listing of Cardiac Assessment Results), I am in agreement with the numbers provided for the frequency of patients with worsening of NYHA classification from first to last assessment.*

None of the patients who had cardiac disease at first assessment and were treated with deferiprone had a worsening of cardiac status while 4 such patients treated with deferoxamine had a worsening of cardiac status, although this difference was not statistically significant. There

was no difference between the 2 arms in the proportion of patients who had an improvement in cardiac status.

Heart disease free survival analysis using the Kaplan Meier method with the log-rank test showed a statistically significant difference between therapy groups in favor of deferiprone as shown in the following figure.

Kaplan-Meier heart disease free survival over the study period



Sponsor figure, CSR, page 45

*Reviewer Comments. I am skeptical about the sponsor's method of the determination of "cardiac disease" and NYHA Class assignment. In my review of Appendix 12.2.7 (Patient Listing of Cardiac Assessment Results), the following questions arose:*

- In the deferoxamine-treated patients, 7 patients (#20, 30, 40, 61, 77, 122 and 154) were classified as NYHA I simply on the basis of a diminution in SF, often of a minimal degree and often transitory.*
- In the deferoxamine-treated patients, 2 patients (#63 and 142) were classified as NYHA I simply on the basis of a transitory diminution in EF of minimal degree.*
- In the deferoxamine-treated patients, 2 patients (#14 and 33) were classified as NYHA I but there was no documentation provided to support the assignment.*
- In the deferoxamine-treated patients, 1 patient (#101) was classified as NYHA Class I because he had had persistently diminished SF and EF from baseline.*
- In the deferiprone-treated patients, 2 patients (#48 and 58) were classified as NYHA I simply on the basis of a transitory diminution in SF of a minimal degree.*

*Since the tables and graph shown above are based on the sponsor's definitions of "cardiac disease" it is incumbent upon the sponsor to provide evidence that a small, and often transitory, decline in either SF or EF or both is a predictor of the development of clinically important cardiac disease or mortality from cardiac impairment.*

*In a telephone conference with the clinical review team on August 17, 2009, the sponsor stated that the assessment of NYHA class was made by the reviewing cardiologist based on clinical information obtained from medical records. Information about these assessments is not included in the NDA. During the telephone conference, the sponsor was asked to provide the cardiologist’s rationale for the assignment of NYHA classification for all of the patients whose classification was questioned by me. The sponsor submitted a response to our request dated September 8, 2009. I re-reviewed the data submitted, and it appears to be a reiteration of the listings in Appendix 12.2.7, and the patients in question above continue to have uncertain reasons for being diagnosed with “heart disease”. In addition, from the sponsor’s recent submission, the following patients should be added to the “uncertain” list: for the deferiprone treated patients (#12-16, 12-171, 12-44, 12-8 and 12-22) and for the deferiprone treated patients (#12-170, 12-42 and 12-67).*

Four patients died during the study period, all of whom were in the deferoxamine treated group. Three of the deaths were said to have been attributed to cardiac events, and all three patients had cardiac disease at entry into the trial. All three had been receiving deferoxamine for less than 1 year during the study period, and compliance appeared to be suboptimal in two of these patients. In 2 patients, cardiac NYHA classification was class II at all observation points, even those most proximate to their deaths. In 1 patient, cardiac disease was NYHA class I, and deteriorated to class IV prior to death. Some of the characteristics of 3 of the patients are shown in the following table.

Features of Patients Who Died from Heart Disease in Study 12-9907

Age at start of review period	Gender	Age of start of first chelation (years)	Chelation therapy during study	Cardiac Disease at Baseline as per NYHA Class	Compliance with chelation (%)	HIC closest to time of death (mg/g wet weight)	% serum ferritin > 2,500 µg/L
26 years	Male	13	DFO	Yes	54	NA	89
23 years	Male	8	DFO	Yes	73	1.004	25
23 years	Female	NA	DFO	Yes	NA	6.100	NA

NA = Not Available; DFO – deferoxamine

\*First assessment of cardiac disease performed at Year 3 of overall review period.

Sponsor table, CSR, page 45

In the fourth patient who died (not listed in the table above), no cardiac disease was documented at any time prior to, or during, the conduct of the trial. He died in a motor vehicle accident.

There were no significant differences in ejection fraction or in shortening fraction from baseline to end of trial for either arm of the trial, nor was there a difference in measurement of these

variables between the 2 arms of the trial, nor was there a difference in the frequency of arrhythmia from first to last assessment between the 2 arms of the trial.

The sponsor conducted an analysis for factors that could be considered to affect cardiac disease in thalassemia patients. These factors and their analyses are shown in the following table.

Comparison of Factors that may Affect Cardiac Disease in Thalassemia Patients

	<b>Ferriprox<sup>®</sup></b> <b>(N = 54)</b>	<b>Deferoxamine</b> <b>(N = 75)</b>	<b>p-value</b>
Percentage of compliance with chelation therapy	89% ± 7% (53)	85% ± 11% (73)	0.0108
Average drug exposure time [years]	5.266 ± 0.843	5.908 ± 0.602	< 0.0001
Mean ± S.D. overall transfusional iron input [mg Fe/kg body weight/day]	0.432 ± 0.076 (53)	0.408 ± 0.085 (71)	0.1106
Mean ± S.D. overall urinary iron excretion [mg Fe/day]	18.8 ± 8.1 (53)	19.3 ± 13.4 (71)	0.8191
Percentage of patients with more than 50% of their serum ferritin results >2,500 µg/L during the review period	35% (19/54)	20% (15/75)	0.0535

Sponsor table, CSR, page 50

The only statistically significant differences in characteristics between the 2 treatment arms were a greater compliance with treatment in the deferiprone treated patients (p=0.0108) and a longer time of treatment in the deferoxamine treated patients (p=<0.0001). There was only limited data available for differences in LIC between the 2 arms. Deferoxamine treated patients tended to have lower LIC measurements during the first several years after commencing therapy compared to deferiprone treated patients, but these differences disappeared during the fourth and succeeding years of the study. Changes in serum ferritin levels over the 5 years of observation were variable, and are shown in the following table:

Mean serum ferritin (µg/L) during the study

<b>Time interval during the study [years]*</b>	<b>Ferriprox<sup>®</sup> (N)</b>	<b>Deferoxamine (N)</b>	<b>p-value</b>
0 – 1	2488 ± 1216 (46)	1967 ± 1624 (59)	0.0631
1 – 2	2291 ± 1079 (47)	1834 ± 1079 (44)	0.0462
2 – 3	2366 ± 1216 (52)	1945 ± 1155 (68)	0.0559
3 - 4	2361 ± 1279 (53)	1886 ± 1208 (70)	0.0373
4 – 5	2377 ± 1337 (50)	2117 ± 1367 (70)	0.3026
≥ 5	2142 ± 957 (49)	2143 ± 1481 (64)	0.9942

Sponsor table, CSR, page 53

There were 2 subgroup analyses performed in the study:

- Subgroup I. This was a subgroup of 107 patients who had had at least 3 serum ferritin determinations in the 3 years immediately preceding entry into the study. The decision to analyze this subgroup was made after the completion of the review period and prior to assessment of any data.
- Subgroup II. This was a subgroup of 94 patients who were matched for age in the 2 therapy groups at the start of chelation therapy.

Both the primary analysis (cardiac disease) and the analyses of factors that could be considered to affect cardiac disease in thalassemia patients in both Subgroups I and II revealed no significantly different results when compared to those of the entire population of the study.

The sponsor concluded that this retrospective study provides evidence that long term therapy with deferiprone results in better cardio-protection in heavily transfused thalassemia patients than does deferoxamine no matter what changes occur in LIC or serum ferritin.

#### 5.3.2.7.4 Safety Evaluation

One hundred and forty nine (149) patients were evaluated in the study. There was no formal collection of safety data. The mean exposure time to deferiprone was 5.27 years (range, 3.52 to 6.1 years) and to deferoxamine was 5.91 years (range, 2.04 to 6.16 years). Total interruption for deferiprone therapy was 1392 days (average, 38.67; range, 3 to 411 days) and for deferoxamine was 865 days (average, 41.19; range 2 to 285 days).

There were 4 deaths observed during the study. These are reviewed above and did not appear to be due to adverse reactions to either medication.

There were no data available regarding serious adverse reactions or clinical laboratory measurements. No differences in medical history were recorded for hypothyroidism, diabetes, nephrolithiasis, cholelithiasis or relative increase in the use of cardiac medications between the 2 groups. The sponsor stated that no new or unexpected diseases surfaced during the study period. There was no difference in the relative increase in the use of cardiac medications between the 2 groups.

#### 5.3.2.7.5 Sponsor Conclusions

From the data generated in this retrospective study, the sponsor concluded the following:

- Deferiprone treatment of thalassemia patients with transfusion related iron overload resulted in a lesser frequency of the development of cardiac disease compared to treatment with deferoxamine.
- This cardioprotective effect of deferiprone did not appear to be due only to improved compliance with therapy compared to deferoxamine.
- Subgroup I analysis suggested no bias because of the inclusion of patients with less than 3 serum ferritin determinations during the 2 years prior to study entry. Subgroup II analysis suggested that age was not a factor in the observed beneficial effects of deferiprone compared to deferoxamine.
- The development of heart disease in this patient population is not predictable based on serum ferritin and LIC measurements.

*Reviewer Comments. There are a number of problems inherent in the interpretation of this study, including the following.*

- *It was retrospective in design.*
- *It derives from the experience of a single institution and, therefore, its broader applicability is uncertain.*
- *Of the excluded patients, 16 were said not to have had chelation therapy for at least 4 years during the chelation period. It is possible that some of these patients had discontinued therapy for adverse reactions or the inability to continue receiving therapy.*
- *LIC measured by SQUID has not been validated and its use in this study is of uncertain value in the determination of body iron load.*
- *Only patients with thalassemia were included in the study. Therefore, the findings from the study may not be applicable to patients with iron overload due to other causes.*
- *It is stated that the cardiologist evaluating the patients was unaware of the treatment employed for each patient. This was an unblinded study and the fact that one of the treatments was oral and the other required the use of an infusion pump might make it difficult not to be aware of the treatment for each patient. In response to a request from the Division for information on the blinding of the cardiologist, the sponsor stated*

*that the cardiologist never actually saw the patient, but made her interpretations solely on the basis of blinded data provided by the investigators who conducted the study.*

- *The lack of improvements in ejection fraction and shortening fraction based on echocardiography in this study are contrary to the improvements reported in patients treated with deferiprone in Study LA 16-0102 (see above).*
- *The diagnosis of “cardiac disease” on the basis of a minimal, often transitory, decrease in SF or EF is not warranted unless such findings can be shown to be predictive of the development of clinical cardiac disease (see Cardiology Consult Review in DARRTS dated April 20, 2009).*

### **5.3.3 Review of Other Studies Submitted**

The other studies submitted by the sponsor are indicated in the table shown at the beginning of this review. None of these studies was believed by the sponsor to be an adequate and well-controlled trial, but the sponsor believes that there is some information provided in each of them that might be useful in assessing the efficacy and/or the safety of the use of deferiprone for the indication.

#### **Study LA01**

This was the initial clinical trial that was performed under the aegis of the current sponsor. The study was designed as a multi-center, open-label, parallel, randomized trial to compare the efficacy of the use of deferiprone (25 mg/kg/tid orally) to that of deferoxamine (50 mg/kg/d 4-7 times/wk) in persons with thalassemia with hemosiderosis due to transfusion therapy. The planned duration of treatment was two years with a one year follow-up period of observation, and patients were stratified on the basis of the severity of the increase in LIC. The study was to be sited at The Hospital for Sick Children (71.8% of subjects were from this institution), The Toronto General Hospital (18.3% of patients), both in Toronto, Canada, and The Montreal Childrens’ Hospital (9.9% of patients) in Montreal, Canada. The investigators were Nancy Oliveri, Gideon Koren and Geoffrey Dougherty. The objectives were to compare the relative effectiveness of the two treatments by determining the following measurements:

- Net negative iron balance as determined by urinary iron excretion.
- Reduction in tissue iron stores as demonstrated by quantification in the liver (by SQUID of the liver), liver biopsy and/or magnetic resonance imaging of the liver, pituitary and heart.
- Reduction in serum ferritin concentration.

The study was also to evaluate the safety of the administration of deferiprone compared to that of deferoxamine.

Seventy-one patients were enrolled (35 in the deferiprone arm, 36 in the deferoxamine arm). Patients ranged in age from 6.9 years to 33.2 years. A total of 14 patients withdrew from the trial before its termination (8 deferiprone, 6 deferoxamine) for a variety of reasons, including adverse reactions. There were many protocol violations, including absence of signed informed consent forms, incorrect timing of baseline studies, incorrect stratification, use of other investigational drugs and non-performance of required assessments. The mean therapy time on deferiprone was 19.7 months (range, 2.6 to 33.3 months) and on deferoxamine was 22 months (range, 8 to 32 months). Efficacy results showed that there were no significant changes in LIC, whether measured by SQUID or by biopsy at any time point up to 36 months after commencing chelation therapy for either therapy. Similarly, there were no significant changes in serum ferritin from baseline to 36 months. Measurement of urinary iron excretion was considered uninterpretable because only 10% of 24 hour urine collections were determined to be adequate for analysis. Twenty-eight percent (28%) of planned blood counts were never performed. Deferiprone was associated with a greater frequency of abdominal pain whereas deferoxamine was associated with a greater frequency of injection reactions. Other adverse reactions were comparable between the two arms of the trial. Two patients receiving deferiprone developed agranulocytosis but recovered after discontinuation of deferiprone.

During the course of the trial, in a companion protocol Study LA-03 below, the primary investigator at The Toronto Hospital for Sick Children and The Toronto General Hospital noted that some patients appeared to develop a refractoriness to the chelation effect on iron excretion with deferiprone as well as increasing hepatic fibrosis in some patients treated with deferiprone. This led to a disagreement between the investigator and the sponsor that eventuated in the sponsor's termination of the trial at the two institutions and the investigator's withholding of data from the sponsor. The ensuing controversy, referred to as the "Oliveri Affair", involved a series of scientific, ethical and political confrontations that have been extensively popularized and have not been completely resolved.

*Reviewer Comments. The sponsor claimed that the trial demonstrated that deferiprone was as effective as deferoxamine in controlling body iron load since serum ferritin and LIC did not increase despite continued iron loading from ongoing therapeutic transfusions. Two of thirty five patients (5.7%) treated with deferiprone developed agranulocytosis. Flaws in the conduct of the study, completeness of data collection and analyses of the data preclude drawing any meaningful conclusions from this study.*

### Study LA02

This was a multi-center, open-label, uncontrolled trial designed to determine the incidence of the development of agranulocytosis and other serious adverse reactions in patients with thalassemia and hemosiderosis due to transfusion therapy who were unwilling or unable to receive deferoxamine therapy and who were treated with deferiprone. Two hundred to two hundred fifty (200-250) patients were to be treated with deferiprone at a dose of 25 mg/kg/tid for one year and prospectively assessed for adverse events. Blood counts were to be performed weekly.

Serum ferritin, alanine aminotransferase (ALT), anti-nuclear, anti-DNA and anti-histone antibodies, and rheumatoid factor were to be obtained at baseline and every 3 months. Serum iron, total iron binding capacity, B- and T-lymphocyte subsets and serum zinc were to be measured at baseline, 6 months and 12 months.

One hundred ninety one (191) patients were screened at 4 hematology centers (Philadelphia, Cagliari, Torino and Ferrara), 187 met the inclusion and exclusion criteria, 25 were withdrawn (21 for adverse reactions) and 162 patients completed the trial. There was no change in mean serum ferritin from baseline to end of study ( $2579 \pm 1777 \mu\text{g/L}$ ,  $2452 \pm 1451 \mu\text{g/L}$ , respectively) for those who completed the study. One patient (0.5%) developed agranulocytosis ( $\text{ANC} < 0.5 \times 10^9/\text{L}$ ) at approximately 15 weeks after commencement of therapy and 9 (5%) developed neutropenia ( $\text{ANC} < 1.5 \times 10^9/\text{L}$ ). All 10 patients had resolution of the hematological abnormalities upon cessation of deferiprone. Other adverse reactions included nausea (16%), vomiting (16%) and arthropathy (13%). ALT values greater than twice the ULN of the reference range were present in 23% of patients at baseline and occurred in an additional 29% of patients during treatment. Most of the elevations in ALT were not associated with symptoms and were more common in persons with antibodies to hepatitis C. Two (2) patients were discontinued from treatment for the increase in ALT and both had resolution of enzyme abnormalities. Mean zinc levels fell from  $14.4 \pm 2.3 \mu\text{mol/L}$  at baseline to  $13.0 \pm 2.1 \mu\text{mol/L}$  at the end of therapy.

*Reviewer Comments. This study was conducted to evaluate safety only, not efficacy. One of 187 patients (0.5%) treated with deferiprone developed agranulocytosis. Gastrointestinal, joint and hepatic adverse reactions occurred. Serum zinc levels fell. Serum ferritin levels and LIC did not increase despite continued iron loading from ongoing therapeutic transfusions.*

#### LA02/LA 06 (for 4 years of followup)

This study was an extension of LA 02 whose objective was to monitor the long term safety and effectiveness of deferiprone administered for an additional 3 years after successful completion of LA 02. The study was initiated to satisfy a request made by the Committee for Proprietary Medicinal Products (European Union) on January 26, 1999 to provide such data. All patients enrolled in LA 02 were invited to enroll in LA 02/LA 06. Serum iron, hematological and hepatic assessments were performed at the same time intervals as for LA 02.

Of the 162 patients who completed the LA 02 trial, 160 elected to be enrolled in the LA 02/LA 06 trial. Of the 160 who enrolled, 84 patients completed 3 additional years of therapy with deferiprone and there were 76 (in addition to the 25 who had withdrawn during the initial year in LA 02) who withdrew during the 3 year extension phase. Total exposure time for the combined LA 02/LA 06 was 531.04 patient years. Patients had a mean age of 18.4 years (range 10 to 41). Three-quarters of the patients were positive for hepatitis C antibody and 40% had been splenectomized.

There was no significant change in mean serum ferritin levels over the 4 years of the trial, even though there were some differences among sites. Eight percent (8%) of patients intermittently discontinued deferiprone because the serum ferritin level fell below 500 µg/L. Twenty-five percent (25%) of patients discontinued deferiprone because of an increasing serum ferritin or LIC level. Patients with baseline serum ferritin levels of >2500 µg/L and patients who had had a splenectomy tended to have a decline in serum ferritin levels while those with serum ferritin levels <2500 µg/L or who had not undergone splenectomy tended to have a rise in serum ferritin levels.

Adverse reactions included nausea (17.1%), vomiting (16.6%) and abdominal pain (13.9%). Twenty-two and one-half percent (22.5%) of patients developed arthropathy. An increase in serum ferritin and an increase in hepatic iron concentration in occurred in 16.6% and 10.7% of patients, respectively. One patient developed agranulocytosis and 16 patients (8.6%) developed neutropenia. Episodes of neutropenia appeared to be more common in non-splenectomized compared to splenectomized patients. Reddish discoloration of the urine was reported by 47.6% of patients and was believed to be due to the excretion of the deferiprone-iron complex.

Eighteen patients withdrew from the trial for various reasons (patient request, often because of a change in residence, 13; protocol violation, 2; unable to comply with weekly blood counts, 2; bone marrow transplantation, 1). Fifty-eight patients were discontinued from the LA 02/LA 06 trial for adverse reactions, 21 during the first year and 37 after the initial year. The reasons for the discontinuation are shown in the following table.

**Table 7-3 Frequency of discontinuation due to adverse events**

Adverse Event	Total
Neutropenia	15
Increased Ferritin	14
Increased Hepatic Iron Concentration	13
Decreased ANC	2
Thrombocytopenia	2
Increased Ferritin and Increased Hepatic Iron Concentration	2
Vomit	2
Hypersplenism	1
Asthenia	1
Nausea	1
Depression	1
Agranulocytosis	1
Increased ALT	1
Hepatitis	1
Arthritis	1
<b>Total</b>	<b>58</b>

Sponsor table, CSR, page 21

Seventy-seven percent (77%) of patients enrolled in the study had previous evidence of hepatitis C at the time of enrollment. ALT levels greater than twice the ULN were present in 23% of patients at baseline and in 25-32% of patients during the remainder of the trial. Thirty-nine (39) episodes of increased serum ALT values were reported in 24 (12.8%) of patients. In 10.2% of

patients, the increases were judged possibly related to deferiprone by investigators. ALT values returned to baseline in most of these patients without changes in the dosing of deferiprone. Two patients discontinued deferiprone because of an increase in ALT values.

There were no significant changes in the proportion of patients with hypogonadism, hypothyroidism, hypoparathyroidism or growth retardation. Cardiac abnormalities were present in 3% of patients at baseline and in 5% (3 cases of cardiomegaly) at last assessment. No changes in physical examination were apparent.

*Reviewer Comments. Extending therapy with deferiprone for an additional 3 years suggested that adverse reactions and efficacy results were similar to those seen during the first year of administration. Lack of apparent efficacy (manifest by a rising serum ferritin and/or LIC) was the major cause for discontinuation of the drug.*

#### LA02/LA 06 (for 7 years of followup)

This study was an extension of LA 02/06 whose primary objective was to monitor the long term safety and effectiveness of deferiprone administered for an additional 6 years after successful completion of LA 02. All patients enrolled in LA 02/LA 06 continued to be followed for an additional 3 years after completion of that study. Serum iron, hematological and hepatic assessments were performed at the same time intervals as for LA 02.

Of the 84 patients who completed a total of 4 years of therapy with deferiprone in the original LA02/06 trial, 57 completed an additional 3 years of therapy without a change in their chelation regimen. Thirteen (13) patients used deferoxamine during this time interval. One hundred and fourteen (114) patients from the original LA02 protocol have had some follow-up data beyond the 4 year time point.

By the end of the 7 year period, mean serum ferritin levels had increased significantly from baseline ( $p=0.0393$ ), which was in contrast to the results found at the end of the 4 year follow-up period. During the 3 year follow-up period of this study, 3 additional patients developed neutropenia. Other adverse reactions occurred at a reduced rate during the follow-up period.

*Reviewer Comments. The data from this study suggest that deferiprone at the dose used had a reduced efficacy in the control of serum ferritin during this extension period but that adverse reactions were little different from those reported previously. The risk of developing neutropenia persisted.*

### LA03

This was a single center (Hospital for Sick Children and the Toronto General Hospital, both in Toronto, Canada), open-label, uncontrolled trial that was originally intended to provide for compassionate use of deferiprone and to collect clinical experience in patients with thalassemia who were unable or unwilling to receive other chelation therapy for transfusion related hemosiderosis. The objectives were to determine long term efficacy (serum ferritin, hepatic and cardiac iron, urinary iron excretion) and long term safety (history, physical examination, hematological and biochemical evaluation) of deferiprone. The source of the drug was peculiar. From the time of first patient enrollment (1989) until October, 1993, the drug was supplied from material manufactured at the [REDACTED] (b) (4). ApoPharma states that it has no data regarding the quality of that (those) batch(es) of drug. Thereafter, the drug was manufactured by ApoPharma under contract for Rh Pharmaceuticals, the original sponsor of the drug. Subsequently, ApoPharma became the commercial sponsor for the drug and continued supplying the drug until it terminated the trial in 1996.

Twenty nine (29) patients were enrolled on the trial and 25 received the drug produced by ApoPharma. Serum ferritin levels fell by an average of  $1868 \pm 2899 \mu\text{g/L}$  from baseline to last observation (periods variable). Patients with serum ferritin levels  $>2500 \mu\text{g/L}$  appeared to have a decreasing trend in serum ferritin levels while those with serum ferritin  $<2500 \mu\text{g/L}$  appeared to have an increasing trend in serum ferritin levels. Mean liver iron concentration (by SQUID or biopsy) decreased by  $5.7 \pm 6.6 \text{ mg Fe/g dw}$  from baseline to last observation. There was no difference in left ventricular ejection fraction at rest or with exercise over the course of the treatment period.

Adverse reactions included arthralgia (28%), nausea (16%) and arthrosis (12%). No deaths occurred. There were 2 adverse reactions that led to drug withdrawal and these included polyarticular arthritis and intractable nausea. Both reactions were ameliorated by discontinuation of the drug. No significant laboratory abnormalities were recorded.

*Reviewer Comments. In this study, adverse reactions reported were similar to those reported in other studies. The efficacy data (decreased level of serum ferritin and decreased LIC) are impressive but are inconsistent in degree with those of most other studies. As with LA 01, this study was terminated early by the sponsor as a result of disagreements with the principal investigator.*

### LA 04 (Compassionate Use Protocol)

This is a study that was designed to provide for the compassionate use of deferiprone for patients with thalassemia or other iron overload conditions requiring chelation therapy and for whom deferoxamine was contraindicated or inadequate. The study was also commenced to assess the

long term safety and efficacy of deferiprone alone or in combination with deferoxamine. It was multicenter and open label. Patients were enrolled at 35 sites in the United States, 9 sites in Canada and 2 sites in Italy. The initiation date was May 23, 1996 and the study remains ongoing. This report for LA 04 covers the treatment period of May 23, 1996 through February 28, 2006.

For enrollment in this trial, requesting physicians were required to obtain regulatory approval for the use of an investigational product (in the United States, an IND number) and to agree to provide ApoPharma with baseline and screening case report forms for each patient. ApoPharma then made a decision as to whether or not the patient qualified for inclusion in the study and, if so, provided the physician with the drug which was administered in accordance with the LA 04 protocol. The usual dose of deferiprone was 75 mg/kg/d in 3 divided doses. Patients were excluded if they had a previous history of severe neutropenia ( $ANC < 0.5 \times 10^9/L$ ), a previous serious adverse reaction to deferiprone, pregnancy or breastfeeding,  $ALT > 3 \times ULN$  or serum creatinine  $\geq 2 \times ULN$ . Patients were required to have weekly blood counts, assessment of adverse reactions and 3-monthly serum ferritin and ALT levels.

Eighty six patients were treated. The age range was 8 to 77 years. There were 33 males and 53 females. The underlying diagnosis was thalassemia in 58 patients and other transfusion dependent disorders in 28 patients (10 with myelodysplastic syndrome, 4 with myelofibrosis, 3 with sickle cell disease and 1 each with aplastic anemia,  $\beta$ -thalassemia/Hgb E, Blackfan-Diamond anemia, chronic lymphatic leukemia, congenital sideroblastic anemia, erythropoietin resistant anemia, pure red cell aplasia, hemolytic anemia, thalassemia intermedia, Aase syndrome and refractory anemia). The mean duration of treatment was 1.3 years (range, 0 to 9.8 years).

There was a decrease in serum ferritin from baseline to last observation of 402  $\mu g/L$  in the treated patients but this change was not statistically significant.

There were 5 deaths. The causes of death were: cardiac failure; multiorgan failure of lungs, liver and kidney; cardiomyopathy; heart failure; and, cardiac disease. None of the deaths was believed by the treating physician to be causally related to deferiprone. Two additional deaths were reported more than one month after deferiprone discontinuation, but the causes of death (progressive MDS with CHF and hepatic failure; and multi-factorial with complications of lung cancer) were said not to be related to the reason for deferiprone discontinuation. Serious adverse reactions included neutropenia (8.14%), agranulocytosis (4.65%) and torsades de pointes (1.16%, one patient). Frequent adverse reactions were nausea (18.6%), fever (16.3%), headache (12.8%) and abdominal pain (10.5%). There were small elevations in the mean ALT from baseline to last observation.

*Reviewer Comments. Serum ferritin levels did not decrease by a statistically significant degree among these patients. Neutropenia and agranulocytosis were not uncommon in this population. This study provides the sponsor's only experience with non-thalassemia patients, and the numbers of the latter are very small and they are a diverse lot.*

### LA08-9701

This was a randomized, open label, controlled, parallel trial in patients with thalassemia and hemosiderosis comparing the safety and efficacy of alternating deferoxamine and deferiprone versus the use of deferoxamine alone for a period of 12 months. The trial was conducted at 2 centers in Italy (Cagliari, Torino) and 1 center in Greece (Athens). The objective was to determine whether or not there was a difference in efficacy and safety in a regimen of alternating deferiprone at a dose of 75 mg/kg/d 5 days a week and deferoxamine at a dose of 20 to 60 mg/kg/d for 2 days a week compared to the administration of deferoxamine at a dose of 20 to 60 mg/kg/d 5 to 7 days a week for a 12 month period. Endpoints included measurement of serum ferritin, SQUID-determined LIC and safety assessments.

Fifty nine patients (29 assigned to deferiprone and deferoxamine, 30 assigned to deferoxamine alone) were treated in the trial. Although there was a small decrease in serum ferritin from baseline to end of the study in both arms of the trial, there was no difference in the decrease between each arm. There was no significant decrease in LIC over the course of the 12 months.

Patients in the combination therapy arm were noted to have more nausea, vomiting, diarrhea and abdominal pain compared to those receiving deferoxamine alone. There were no significant changes in laboratory values in either arm.

*Reviewer Comments. This study suggests that, other than for the reduction in the need for daily deferoxamine infusions by 3-5 days/week, there was no greater efficacy of the use of the two drugs in combination compared to the administration of deferoxamine alone.*

### LA10-9902

The objective of this study was to compare lymphocyte clastogenicity (measuring chromosomal aberrations) in patients with thalassemia when they were switched from deferoxamine to deferiprone and vice versa. It was an open-label, single-center, single crossover study performed in Cagliari, Italy between September 29, 1999 and August 29, 2000. Ten patients were enrolled in the trial and received deferoxamine (20-60 mg/kg/d 4 to 7 days a week) for 20 days then switched immediately to a 20 day course of deferiprone (75 mg/kg/d). Ten additional patients received the exact same treatment but in reverse order.

No efficacy data were collected. There was a single adverse reaction reported. One patient was admitted to a hospital for a severe episode of migraine that occurred approximately one month after having chelation therapy switched to deferoxamine. The reaction abated within 5 days.

Data from the study indicated a similar frequency of chromosomal abnormalities in persons treated with either drug.

*Reviewer Comments. This study provides no information for the efficacy and minimal information for the safety of the use of deferiprone.*

#### LA11

This was an investigator initiated trial to determine the efficacy of deferiprone in the prevention of iron mediated oxidation of red blood cells and platelet membranes in patients with thalassemia-Hemoglobin E disease. It was an open-label, uncontrolled trial at a single institution in Thailand performed between April 8, 2000 and December 24, 2002.

Twenty four (24) patients who were not transfusion dependent, or only irregularly transfused, were enrolled. The mean age of the patients was  $33 \pm 11$  years (range 17 to 63) and 66.7% were males. Deferiprone was administered at a mean daily dose of  $48 \pm 5.7$  mg/kg (range 15 to 78) for a mean of  $344 \pm 179$  days (range 5 to 536). Sixteen patients were treated for more than 1 year.

Twenty (20) patients who had at least a prior and end of treatment assessment had a decrease in mean serum ferritin from  $3287 \pm 1927$   $\mu$ g/L to  $1221 \pm 1667$   $\mu$ g/L. LIC in 16 patients with repeat studies declined from  $20.1 \pm 8.4$  mg/g dw to  $7.5 \pm 7.0$  mg/g dw.

Adverse reactions included nausea (42%), diarrhea (29%), anorexia (13%), fever (13%) and vomiting (8%). There was one case of neutropenia, but agranulocytosis did not occur. A 27 year old splenectomized male died from food poisoning, diarrhea and sepsis but the investigator did not attribute the adverse reactions to deferiprone. Drug withdrawal was occasioned in 3 patients: one patient developed bilateral renal calculi with hydronephrosis and renal dysfunction (Cr, 6.1 mg/dl) which improved after stent placement; one patient with an elevation in serum creatinine (6.3 mg/dL); and one patient became pregnant.

There is no comment in the sponsor's report of the findings for the primary objective of the trial.

*Reviewer Comments. The population studied in this trial was different from the populations in the other trials submitted by the sponsor. These were Thai patients with thalassemia-Hemoglobin E disease who had either no or limited transfusion requirements. Efficacy evaluation was not the primary endpoint of the trial. The decreases in serum ferritin levels and the LIC are impressive, but this may be because there was little transfusional iron loading during the year of the trial. The frequency of the development of diarrhea and the death from diarrhea in one patient, even though the death was not attributed to the drug, is disconcerting.*

## LA 15-0002

This was a single center, open-label, uncontrolled trial of the safety and efficacy of the use of deferiprone at a dose of 75 mg/kg/d for 3 months for the treatment of iron overload in subjects with transfusion-dependent thalassemia in Iran. Twenty-nine patients with thalassemia and a serum ferritin greater than 2500 µg/L were enrolled. Efficacy was determined by periodic serum ferritin measurements. Safety was assessed by monitoring adverse reactions and laboratory studies.

Over a 3 month period, the mean serum ferritin fell from  $3364 \pm 900$  µg/L at baseline to  $1271 \pm 302$  µg/L. Adverse reactions included gastrointestinal symptoms, asthenia, arthralgia and somnolence. One patient developed neutropenia ( $ANC 1.45 \times 10^9/L$ ). Two patients withdrew because of adverse reactions (arthralgia, neutropenia). A third patient withdrew because she thought the drug would cause skin discoloration.

*Reviewer Comments. The decrease in serum ferritin after only 3 months of therapy is different from most studies with virtually all other iron chelators, including previous studies with deferiprone. The study population was from a single country and the results may reflect peculiarities of the treatment of such populations and may not be applicable to other populations. There was no record of the number of transfusions administered to patients during the trial, and it is possible that the fall in serum ferritin was related to an infrequency in the rate of transfusions. No other assessments of body iron burden were performed. No new adverse reactions were reported.*

## Borgna-Pignatti Study

This was a retrospective, “controlled” observational study that evaluated all patients with thalassemia major born between 1970 and 1993 and seen at 8 of the major thalassemia treatment centers in Italy. The observational period was January 31, 1995 to December 31, 2003. The initial date was selected because that was the approximate date on which deferiprone began to be used in clinical trials and subsequently was available by prescription after approval in Europe. At the outset of the study, enrolled patients could not have had a cardiac event and on follow-up could not have had a bone marrow transplantation. All patients must have been receiving chelation therapy throughout the study period.

Five hundred and sixteen (516) patients met the entry criteria. Of those, 359 patients received only deferoxamine (30-50 mg/kg/d 5-6 times weekly) and 157 were converted to deferiprone (75 mg/kg/d) at some time before the end of the study. Beginning in July, 2001, some patients were enrolled in clinical trials with deferasirox. The primary efficacy endpoint was the incidence of cardiac events (not otherwise defined) by treatment group for each calendar year. Time zero was January 31, 1995. The definition of group for each year was based on the treatment that the patient was receiving on January 1 of the given year. The statistical method used was a time-to-

event analysis, where an event was defined as a cardiac complication. Secondary endpoints included death from all causes, rate of change in serum ferritin, effect of gender, birth cohort, and serum ferritin levels at baseline on the incidence of cardiac events, and the rate of events relative to person-years of exposure to each chelator. Safety was assessed by adverse event reporting. Serum ferritin levels were measured at least 3 times a year.

Demographic characteristics were similar between the 2 arms of the study except that there were more patients with serum ferritin levels >2500 µg/L among patients converted to deferiprone. There were 52 cardiac events (14.5% of all patients) during the observation period, 10 of which were cardiac deaths. Of the surviving 42 patients who experienced a cardiac event after entry into the study, 5 died of cardiac disease within 4 to 47 months after the first cardiac event. At the time of the event, all patients were receiving deferoxamine. Six events occurred in patients who had received deferiprone, but who had reconverted to deferoxamine for between 1 year and 8 months to 5 years and 4 months before the event. Eight patients were converted to deferiprone after the development of a cardiac event. The incidence of cardiac events while receiving deferoxamine per 100 patient-years was 0.6 in 1995 to 3.4 in 2003. Based on total exposure, there were 1.4 events per 100 person-years in patients receiving deferoxamine and 0 events per 100 patient-years in patients receiving deferiprone. Two patients receiving deferiprone died of non-cardiac deaths (see below) during the observation period. In general, serum ferritin levels were lower in patients receiving deferoxamine compared to those receiving deferiprone. Age at entry was a predictive risk factor for the development of cardiac events, as each increasing year of age was associated with a hazard ratio of 1.17 (p<0.01).

Forty-six (46, 31%) patients discontinued deferiprone due to the development of an adverse reaction: increase in serum ferritin or LIC (21 patients); arthropathy (10); neutropenia (8); agranulocytosis (1); increase in ALT (2); gastric discomfort (2); worsening of renal failure (1); and worsening of hepatic insufficiency (1). An additional 16 patients discontinued deferiprone for other reasons including: lack of compliance with weekly blood count schedule (6); end of deferiprone clinical trial (3); fear of adverse reactions (2); entered deferasirox trial (3); and, unknown (3). Twenty-six (26, 5%) patients died during the observation period, 24 in the deferoxamine group and 2 in the deferiprone group. Of the deaths in the deferoxamine group, 15 were cardiac related. In the deferiprone group, 1 died of an automobile accident and 1 died of a catheter related infection. The latter did not have neutropenia at the time of death.

*Reviewer Comments. This study was observational in design and, therefore, should be hypothesis-generating and allows very limited inference. Nonetheless, the difference in cardiac events and cardiac deaths in patients treated with deferoxamine or deferiprone is striking. Once again, data suggest that deferiprone has less of an effect on lowering serum ferritin when compared to deferoxamine, but, paradoxically, cardiac morbidity and mortality may be reduced by treatment with deferiprone. No new safety concerns were elucidated.*

*In response to a request from the Agency, the sponsor indicated that 86 subjects that were reported in this study were also included in the patient population reported in Study LA 12-9907(supportive study reviewed above) and that 57 subjects reported in this study were also included in Study LA 17-9701 (see immediately below) .*

LA 17-9701

This study is submitted in the form of a publication that appeared in the British Journal of Hematology (2002. 118:330-336) and is entitled “The safety and efficacy of deferiprone in a large-scale, 3-year study in Italian patients”. The paper is based on a special program created by the Italian Ministry of Health during the 3 year period prior to the commercial availability of deferiprone in 2000. The program allowed the Ministry to supervise the distribution of deferiprone to all patients in the country while monitoring its efficacy and safety. The controlled distribution was for the treatment of iron overload in patients with thalassemia who presented with serious toxicity from deferoxamine therapy. Efficacy was determined by periodic measurement of serum ferritin, and safety was assessed by periodic blood counts and ALT.

The registry of treated patients was managed by a panel of physicians skilled in the management of thalassemia. The panel designed the study protocol and managed the collection of data. Enrollment required a request from the patient’s physician with a description of the medical history and the reason why deferiprone was needed. Inclusion criteria were age >6 years, serious toxicity with deferoxamine and serum ferritin >2000 µg/L or LIC >4 mgFe/g dw. Exclusion criteria were serious toxicity with previous deferiprone use, administration of other drugs that might induce neutropenia, previous unexplained episodes of neutropenia and serious co-morbid conditions. Patients were treated with deferiprone at a dose of 75 mg/kg/d. Laboratory monitoring was conducted at periodic intervals. Interruption of therapy was recommended if the serum ferritin fell below 500 µg/L, the total white blood cell count fell to <1.5 x 10<sup>9</sup>/L or there was an elevation of serum ALT. Patients were evaluated for safety and efficacy at the end of each 12 month treatment period through 36 months from the time of enrollment. Analyses were carried out only for patients who completed 3 years of therapy and for whom there was no missing data (a total of 151 patients).

There were 577 requests for enrollment and the panel accepted 532 patients from 86 thalassemia centers between July, 1997 and July, 2000. Treatment was actually given for from 3 to 36 months. Mean age at enrollment was 21.3 years (range, 6 to 54 years, and one patient with thalassemia intermedia who was 70 years old). Splenectomy had been performed in 52.4% of enrollees. The mean baseline serum ferritin was 2866 ± 2188 µg/L with 59% of patients having a serum ferritin in excess of 2000 µg/L. Over the 3 year period, 77.3% of patients continued on the prescribed dose of deferiprone, 20.7% experienced interruptions or discontinued deferiprone and 2% died. Of the 11 deaths, 9 were due to heart failure, 1 was due to cerebral hemorrhage and 1 was due to an automobile accident. One hundred and sixty-eight patients (168) received at least 3 years of therapy. Agranulocytosis occurred in 5 patients at between 5 and 13 months after commencement of therapy. All resolved after drug withdrawal and none was rechallenged. Eighteen (18) patients developed neutropenia at from 10 to 775 days of therapy with resolution of neutropenia occurring from a range of 2 to 92 days. Five (5) patients were rechallenged and, of these, 1 developed recurrent neutropenia after 10 months. Additional common adverse drug reactions included gastrointestinal symptoms and arthropathy. Of the 151 patients who received therapy for at least 3 years, the mean serum ferritin levels at baseline, and after 12, 24 and 36 months, respectively were 2579, 2671, 2472 and 2320 µg/L. The patients whose initial serum ferritin was >2000 µg/L demonstrated a greater fall in serum ferritin levels over time compared

to those whose serum ferritin was <2000 µg/L at baseline. There were no significant changes in serum ALT overall during the course of the study, but elevations in ALT led to an interruption in administration of deferiprone in 12 patients, 4 of whom eventually discontinued the use of deferiprone. The study did not investigate the issue of the development of hepatic fibrosis.

*Reviewer Comments. This was an observational registration study that allowed for the availability of deferiprone treatment for patients with hemosiderosis and thalassemia who could not benefit from deferoxamine prior to the marketing of the deferiprone (in essence, a Treatment Protocol). Although there appeared to be a small decrement in serum ferritin in patients who completed all 3 years of drug administrations, there was no change in serum ferritin to end of treatment for the entire treated population, probably because many discontinued deferiprone treatment for adverse reactions or lack of response. Adverse reactions were similar to those reported in other studies.*

*As noted above, some of the patients reported in this study were also reported in the Borgna-Pignatti study. Additionally, 8 subjects were common to Study LA 12-9907, Borgna-Pignatti and this study.*

## **6 Review of Efficacy**

### **6.1 Efficacy Summary**

The pivotal study submitted in support of the efficacy of the use of deferiprone for hemosiderosis due to transfusion therapy in persons with thalassemia was LA 16-0102. The main “other supportive” study was LA 12-9907. Both of these studies are reviewed extensively above. In addition, all of the other studies submitted in support of the application for the NDA are reviewed above. This section will provide a summary of the efficacy findings.

For Study LA 16-0102, the claimed primary efficacy endpoint was the change in the MRI T2\* as a measure of cardiac iron concentration from baseline to end of study at 12 months, comparing deferiprone to deferoxamine. Although there were “statistically significant” increases in the number of milliseconds in the MRI T2\* measurements in the deferiprone-treated patients compared to the deferoxamine-treated patients, the sponsor has provided minimal documentation that relates the MRI T2\* measurement to chemically determined cardiac iron concentration documented by standard tissue assays of iron as obtained by biopsy or at autopsy. In addition, the sponsor has not provided any evidence of a correspondence between the quantitative changes in MRI T2\* and clinical benefits as exemplified by reduction in death or clinically significant morbidity in the patients in whom there was an improvement in MRI T2\*. Rather, this study appears to be an elegant working hypothesis of a potential mechanism of action of deferiprone

that should encourage further clinical study of the drug as an iron chelator. It should be noted here that Study LA 16-0102 was not conducted under the IND, and, in fact, had been completed before the sponsor ever discussed it with the FDA. At the time of the discussion with the Review Division, the Division expressed concern as to the appropriateness of the primary efficacy endpoint selected by the sponsor, and made clear to the sponsor that the clinical relevance of the efficacy endpoint would have to be supported by adequate evidence before it could be accepted as valid. This the sponsor has not done.

There were additional problems with the interpretation of Study LA 16-0102. These included the following:

- Measurements of changes in serum ferritin and LIC have been the generally accepted methods of evaluation of the efficacy of therapy in persons with iron overload. In Study LA 16-0102, these measurements were secondary efficacy endpoints.
- In Study LA 16-0102, SQUID was used to measure LIC. SQUID biosusceptometry is known not to accurately measure LIC demonstrated by biopsy. Generally, there is a 1:2 ratio of iron concentration between SQUID:biopsy results (see Exjade Advisory Committee transcript, September 29, 2005). SQUID may be useful in the measure of changes in LIC.
- The trial was restricted to patients with thalassemia major. The results may not be applicable to other populations. The inclusion criteria did not mention any of the standard assessments for body iron stores (serum ferritin, LIC). The age range was compressed and did not include any pediatric patients. All patients with any evidence of heart disease were excluded. Therefore, the results can be extrapolated to only a very small segment of the possible targeted treatment population.
- Eighty six (86) patients with thalassemia from a total of 160 patients who otherwise met the criteria for enrollment on the study were excluded because their MRI T2\* was either <8 ms (11 patients) or >20 ms (75 patients). Therefore, more than half of all patients for whom the indication is proposed were excluded from the study.
- Enrollees in the deferoxamine arm were more likely to have demographics that suggest a more impaired population including:
  - Older age, thereby likely to have received a larger lifetime iron load because of more transfusions
  - Greater frequency of splenectomy, suggesting more severe disease
  - Higher mean baseline serum ferritin and greater percent of persons with serum ferritin in excess of 2500 µg/L, suggesting a larger lifetime iron load and a poorer response to deferoxamine prior to enrollment on the trial (all subjects were previously being treated with deferoxamine)
- The dose of deferiprone used in this trial (100 mg/kg/d) was atypical. For most of the other studies performed by the sponsor, the usual total daily dose was 75 mg/kg/d.
- The mean dose of deferiprone actually administered in the trial was 92 mg/kg/d, which is less than the maximally recommended dose in the proposed label.
- The mean dose of deferoxamine actually administered in the trial was 43 mg/kg/d, which is less than the maximal commonly used dose of deferoxamine (50 mg/kg/d) and the

planned dose for the trial. Therefore, some of the claimed beneficial comparative effects of deferiprone might have been due to suboptimal dosing with deferoxamine.

- The LVEF and LVSF were normal throughout the trial in almost all patients. Small changes in these measurements that are all within the normal range may have no clinical significance. Consultation was requested from the Division of Cardiovascular and Renal Drug Products regarding the utility of measuring periodic LVEF and LVSF as a means of determining the clinical significance of a therapeutic intervention in persons with potential cardiac impairment. The response was provided by Drs. Shari Targum and Norman Stockbridge (see DAARTS, April 20, 2009). The following points were made:
  - The reviewer was unable to evaluate the clinical meaningfulness of small changes in ejection fraction or fractional shortening.
  - Meaningful clinical outcomes (e.g., heart failure, heart failure hospitalizations, mortality) should be used as the basis for a claim for reducing heart failure incidence.
  - Measurements of LVEF and LVSF are subject to inter-reader and intra-reader variability as well as reader expertise. It would be of interest to understand how these imaging studies were read.
  - LVEF and LVSF are measurements that can be influenced by loading conditions.
  - If the image readers were aware of the drug therapy in this open-label trial, then potential bias cannot be excluded.
- There was no significant improvement from baseline to end of study in serum ferritin or SQUID measurements of LIC in patients treated with deferiprone.

There were also problems in the evaluation of Study LA 12-9907 as support for the efficacy and safety of the use of deferiprone for the proposed indication. These include the following features of the study:

- The study was a single center, retrospective, non-randomized study.
- The study included patients with thalassemia only.
- The dose of deferiprone actually received by patients in the study varied from 35 to 100 mg/kg/d rather than the dose proposed in the label
- The dose of deferoxamine actually received by patients in the study was 19 to 60 mg/kg/d for 4 to 7 days per week. These doses may have been less than the most effective dose for a given patient and may have biased the results against deferoxamine.
- Patients receiving deferoxamine were older and had commenced chelation therapy at an older age. These demographic features may have affected the results of the deferoxamine treated patients. It is noted that deferoxamine treated patients tended to have lower serum ferritin levels, lower LIC by SQUID and fewer serum ferritin levels above 2500 ng/mL at entry.

- The lack of improvements in ejection fraction and shortening fraction based on echocardiography in this study are contrary to the improvements reported in patients treated with deferiprone in Study LA 16-0102 (see above).

The efficacy results from the other trials were as follows:

- LA 01. There was no decrease from baseline to up to 36 months of therapy with deferiprone in serum ferritin or LIC measured by SQUID or by liver biopsy. Evaluation of another endpoint, urine iron excretion, could not be determined because only 10% of urine samples were adequate for measurement.
- LA 02. This study was designed to evaluate only the safety, not the efficacy, of the administration of deferiprone. During the course of the study, however, serum ferritin was regularly measured. There was no decrease in serum ferritin levels over the course of up to 12 months of observation.
- LA 02/06 (3 additional years). During 3 additional years of therapy with deferiprone, patients originally enrolled in the LA 02 trial did not have a decrease in serum ferritin levels. Of patients who discontinued deferiprone, 8% temporarily discontinued deferiprone because of an excessive diminution of serum ferritin, while 25% permanently discontinued the drug because of evidence of increased serum ferritin or LIC. About half of the discontinuations appear to be due to lack of efficacy.
- LA 02/06 (3 additional years beyond completion of LA 02/06 for 3 additional years). Serum ferritin levels increased during an additional 3 years of observation.
- LA 03. In patients treated for variable periods of time with deferiprone, serum ferritin levels fell by a mean of  $1868 \pm 2899$   $\mu\text{g/mL}$  and LIC (by biopsy or SQUID) fell by a mean of  $5.7 \pm 6.6$  mg Fe/g dw. No changes occurred in cardiac ejection fraction over the course of the trial.
- LA 04 (Compassionate Use Protocol). In patients treated with deferiprone for from 0 to 9.8 years (median, 1.3 years), the serum ferritin fell by a mean value of  $402$   $\mu\text{g/L}$  but this difference was not statistically significant.
- LA 08-9701. In this study that compared the efficacy of the use of deferoxamine alone with that of the combined use of deferoxamine and deferiprone, there was a small decrement in serum ferritin that was no different in both arms and there was no decrease in LIC with either treatment over a period of 1 year.
- LA 11. In this study of patients with Hgb E-thalassemia who had either no, or only a minor, transfusion dependency, and who were treated with deferiprone at an average dose of  $48$  mg/kg/d for 1 year, there was a decrease in mean serum ferritin from  $3287 \pm 1927$   $\mu\text{g/L}$  to  $1221 \pm 1667$   $\mu\text{g/L}$  and a decrease in LIC from  $20.1 \pm 8.4$  mg/g dw to  $7.5 \pm 7.0$  mg/g dw.
- LA 15-0002. In this study, patients with thalassemia were treated with deferiprone at a dose of  $75$  mg/kg/d. Over a 3 month period, the mean serum ferritin fell from  $3364 \pm 900$   $\mu\text{g/L}$  at baseline to  $1271 \pm 302$   $\mu\text{g/L}$ .
- Borgna-Pignatti Study. Although patients treated with deferoxamine had lower serum ferritin levels compared to those treated with deferiprone, there were no cardiac events in

deferiprone treated patients (157) compared to 52 cardiac events (14.5% of patients), including 10 cardiac deaths, in deferoxamine treated patients (359).

- LA 17-9701. In this registry, patients with thalassemia were treated with deferiprone at a dose of 75 mg/kg/d for 3 to 36 months. Eleven (11) patients died, 9 due to heart failure. For those who completed 36 months of treatment, serum ferritin levels fell from a mean of 2579 to 2320 µg/L. Overall, however, there was no decrease in all treated patients, a number of whom discontinued treatment due to the development of various adverse reactions.

*Reviewer Comments. The sponsor has studied deferiprone for use in treating transfusional hemosiderosis in thalassemia patients. The evidence for efficacy in these studies is very thin or lacking or not based on the usual measures of success in the treatment of hemosiderosis in thalassemia. I am well aware that the standard methods of assessing treatment success in transfusion-dependent hemosiderosis (serum ferritin, liver iron concentration) are quite imperfect. In fact, because of that, the approval granted deferasirox was accelerated, rather than full, even though deferasirox administration was associated with a decrease in serum ferritin and LIC in the many populations studied (thalassemia, sickle cell anemia, myelodysplastic syndrome, other anemias). The Division has required the sponsor of deferasirox to perform post-marketing studies to show that the standard measures of body iron load, when improved by administration of deferasirox, lead to an improvement in mortality or important morbidity in these patients.*

*The data provided for the efficacy of the treatment of transfusion related hemosiderosis in patients for whom the sponsor has directed the indication is lacking. In almost all of the studies performed, all of the patients had thalassemia and, therefore, the efficacy data can only be applied to that group of patients. In the determination of benefit for non-thalassemia patients, there would have to have been some significant representation of other populations, and there simply is not.*

*In almost none of the submitted studies of the efficacy of deferiprone is there evidence that serum ferritin or LIC are decreased in any meaningful way. The exceptions to that statement are found in Study LA 03, LA 11 and LA 15-0002. These 3 studies, however, have some striking differences (small numbers, hemoglobin E-thalassemia with little or no transfusion dependency, results simply not consistent with other studies) from the majority of the studies performed with deferiprone, and appear to be at odds with the results reported in the larger and longer studies of deferiprone.*

*I can only conclude that the sponsor's data do not provide adequate or substantial evidence for the efficacy of the use of deferiprone in persons with thalassemia and hemosiderosis due to transfusion therapy. No conclusions whatsoever can be made regarding the efficacy or safety of deferiprone in non-thalassemic patients with transfusion-related hemosiderosis because, other than for very limited data collection in a few patients enrolled in a treatment protocol, these patients were not studied by the sponsor.*

## 7 Review of Safety

### 7.1 Methods

#### Safety Summary

The safety assessments from the “pivotal” and the “supportive” study as noted above are of little use in determining adverse reactions that might be associated with the use of deferiprone because the number of patients exposed to deferiprone was too small in Study LA16-0102 (29 subjects) and because there was no systematic collection of adverse reactions in Study LA12-9907. Because of this, and because the drug has been administered to humans for more than 20 years, I have reviewed the Summary of Clinical Safety (Module 2, Section 2.7.4) in an effort to determine the absolute and relative risks of the use of deferiprone. It is, therefore, not possible to use the standard review format for the report in its entirety, and, where necessary, deviations from the format will be indicated.

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The following data have been reviewed to evaluate the safety of deferiprone:

- ApoPharma sponsored studies (LA 01, LA 02/06, LA 08-9701, LA 10-9902, LA 12-9907, LA 14-9907, LA 15-0002, LA 16-0102, LA 20-BA and LA 21-BE).
- Independent investigator driven studies (LA 11, Borgna-Pignatti study).
- Compassionate use programs (LA 03, LA 04/LA 06B).
- Italian Ministry of Health Active Drug Surveillance Program (LA 17-9701).
- Postmarketing pharmacovigilance data.

The major features of these studies are shown in the following tables from the sponsor’s submission.

Clinical Review  
 George Shashaty  
 NDA 21825  
 Ferriprox (deferiprone)

Study ID Location in Module 5	Centers Location(s)  Study Start; Study End; Study Duration	Design Control type  Primary Objective	Study and Control Drugs Dose, Route, and Regimen	No. of Subjects by Arm (Entered/ Completed) Sex (M/F) Diagnosis Inclusion Criteria	Major Findings
LA16-0102  5.3.5.1	4; Greece, Italy  Jan 2003; Oct 2004; 1 year	Multicenter, randomized, open-label, active control  To determine whether orally administered DFP exhibits superior efficacy in removing excess iron from the heart compared with that of standard s.c. infusions of DFO, as reflected by MRI T2* assessments of the heart in subjects treated with either chelator.	DFP: oral; 33.3 mg/kg body weight t.i.d.  DFO: s.c.; 50 mg/kg infused 5 to 7 times per week	DFP: 29/27  DFO: 32/29  M and F  Thalassemia major	<b>Major Findings</b>  This study showed that DFP is superior to DFO in decreasing cardiac iron overload, as measured by MRI T2*. At baseline, the difference of the geometric means (the anti-logs of the means of the log MRI T2* data) of the DFP (13.0 ms) and DFO (13.3 ms) treatment groups was not significant (p = 0.77). The geometric mean increased to 15.4 ms after 6 months, and to 16.5 ms after 12 months of treatment with DFP, with a significantly greater percentage increase from baseline compared to subjects treated with DFO (18% vs. 9%, p = 0.0404 [6 months]; 27% vs. 13%, p = 0.0228 [12 months]).  This study also showed greater beneficial effect of DFP (vs. DFO) on cardiac function, as measured by absolute changes from baseline to 12 months for LVEF by CMR (DFP: 3.07% ± 3.58%, n = 29; DFO: 0.32% ± 3.38%, n = 31; p = 0.0034), for LVEF by ECHO (DFP: 2.50% ± 6.04%, n = 28; DFO: -0.56% ± 4.90%, n = 31; p = 0.0358), and % change from baseline to 12 months for LVSF by ECHO (DFP: 5.82 ± 15.62, n = 29; DFO: -2.64 ± 10.65; n = 32; p = 0.0180).  Comparable reductions in LIC and serum ferritin values were recorded in DFP and DFO treatment groups. After 12 months of treatment, the LIC of subjects treated with DFP and DFO showed mean reductions of 0.93 mg Fe/g dw liver and 1.54 mg Fe/g dw liver, respectively. The difference was not statistically significant (p = 0.3961). For serum ferritin, there was a decrease from baseline to 12 months in both the DFP and DFO groups (-181.0 µg/L vs. -466.1 µg/L, respectively). Again, the difference was not significant between the two groups (p = 0.1598).  Therapeutic compliance was comparable between the DFP and DFO treatment groups (93.7% vs. 93.2%), indicating that differences in efficacy between the two groups is not attributable to differences in treatment compliance.  Safety: No subjects experienced agranulocytosis. There was one episode of neutropenia of mild severity possibly related to DFP, which resolved without discontinuation of the therapy. The majority of AEs and ADRs were mild to moderate in intensity.

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LA12-9907  5.3.5.1	1; Italy  Jan 1995; Mar 2001; At least 4 years	Open-label, parallel, longitudinal, active controlled single center  To evaluate incidence and progression of cardiac disease and survival in patients treated with Ferriprox compared with DFO over the same period of time	Arm A (DFP): oral; 75 mg/kg/d, 7 d/wk  Arm B (DFO): s.c.; 20 to 60 mg/kg/d, 4 to 7 d/wk	Arm A: 54 Arm B: 75  As the study assessed already existing data, no study completion or withdrawal were defined.  M and F  Transfusion-dependent thalassemia major; ≥5 years old at time of start of review period	<b>Major Findings</b>  At the end of the study, 7 subjects (13.0%) in the DFP group had cardiac disease (NYHA Class I, II, III, or IV) compared with 22 subjects (29.3%) in the DFO group. Newly diagnosed cardiac disease was observed in 13 (20.6%) of the 63 DFO-treated subjects who were initially cardiac-disease free at the first study assessment, and in two (3.7%) of the 47 DFP-treated subjects who were cardiac-disease free at the first study assessment (p = 0.0133). Overall, worsening of preexisting cardiac dysfunction or newly diagnosed cardiac disease was observed in two subjects in the DFP group and in 15 subjects (20%) in the DFO group (p = 0.0069). Improvement in NYHA class was observed in three of seven (43%) DFP-treated subjects compared with three of twelve (25%) DFO-treated subjects with cardiac disease at first assessment; the difference, however, was not statistically significant.  Subjects in the DFP group had significantly longer cardiac disease-free survival compared with subjects in the DFO group. Kaplan-Meier analysis of cardiac disease-free survival over a 5-year period was significantly more favorable in the DFP group (p = 0.003). By the end of the study, the two treatment groups did not show significant differences in mean serum ferritin concentrations (p = 0.994).  Four subjects, all treated with DFO, died during the study period; three had cardiac disease at first assessment, and death was attributed to irreversible progression of cardiac dysfunction. The fourth subject died within a few hours of being admitted to a provincial hospital for acute abdominal pain. No cause of death for this subject was provided to the sponsor.  Mean compliance was 89 ± 7% (n = 53) with DFP, and 85 ± 11% (n = 73) with DFO. Therefore, less favorable clinical outcomes in the DFO-treated group cannot be attributed to lack of compliance.

Study ID Location in Module 5	Centers Location(s)  Study Start; Study End; Study Duration	Design Control type  Primary Objective	Study and Control Drugs Dose, Route, and Regimen	No. of Subjects by Arm (Entered/ Completed)  Sex (M/F) Diagnosis Inclusion Criteria	Major Findings
LA-02/06  5.3.5.2	4; Italy, U.S  Feb 1995; Oct 2002 7 years	Multicenter, open-label, uncontrolled  To monitor long-term safety and effectiveness of a fixed dose of DFP	DFP: oral; 25 mg/kg body weight t.i.d.	187/70  M and F  Iron -loaded subjects with thalassemia	<p>In 162 subjects who completed 1 year of therapy, mean serum ferritin concentrations at baseline and at 12 months were similar (<math>p = 0.26</math>). Ferritin values at baseline and at termination for all DFP recipients, whether or not they completed the study (intent-to-treat analysis), were also similar (<math>2,696 \pm 1,877 \mu\text{g/L}</math> and <math>2,633 \pm 1,815 \mu\text{g/L}</math>, respectively; <math>p = 0.58</math>).</p> <p>For 84 subjects who completed 4 years of study, mean serum ferritin was <math>2,268 \pm 1,529 \mu\text{g/L}</math> at baseline and <math>2,087 \pm 1,386 \mu\text{g/L}</math> after 4 years (<math>p = 0.338</math>). For subjects with initial ferritin levels greater than <math>2500 \mu\text{g/L}</math>, the ferritin level declined from <math>3661 \pm 1862 \mu\text{g/L}</math> at baseline to <math>2630 \pm 1708 \mu\text{g/L}</math> at the end of 4 years (<math>p = 0.038</math>). For subjects with initial values less than <math>2500 \mu\text{g/L}</math>, the mean ferritin level did not change significantly.</p> <p>A total of 57 subjects completed up to 7 years without change in chelation regimen. Analyses of efficacy were based on the intent-to-treat population because of the relatively small number of subjects remaining at 7 years. Overall, serum ferritin values increased by a small but statistically significant amount from baseline to the seventh year of DFP treatment (<math>p = 0.0395</math>). Further increase in ferritin beyond that seen at 48 months was small, representing 2.8% of mean baseline concentrations. The slope of the overall trend of serum ferritin for the ITT population, including all subjects and using the last observation carried forward for missing values, was estimated to be <math>3.2 \pm 1.8 \mu\text{g/L/month}</math>, which was not significantly different from zero. The results of the trend analysis are comparable to those in the 48-month analysis.</p> <p>In total 20 of the 187 subjects developed an SAE of neutropenia or agranulocytosis during the trial. Seventeen of the 20 subjects who experienced neutropenia had not been splenectomized. The difference in incidence of neutropenia or agranulocytosis was significant between the two groups of subjects (<math>p = 0.0034</math>); 2.7% and 15.9% of splenectomized and nonsplenectomized subjects respectively.</p>

Study ID Location in Module 5	Centers Location(s)  Study Start; Study End; Study Duration	Design Control type  Primary Objective	Study and Control Drugs Dose, Route, and Regimen	No. of Subjects by Arm (Entered/ Completed)  Sex (M/F) Diagnosis Inclusion Criteria	Major Findings
LA08-9701  5.3.5.1	3; Italy, Greece Sep 1998; Feb 2001; 12 months	Multicenter, open-label, randomized, parallel, active controlled  Evaluate efficacy and safety of alternating use of DFP and DFO compared with current standard therapy with DFO in treatment of iron overload	DFP (25 mg/kg t.i.d. oral, 5 d/wk) and DFO (20 to 60 mg/kg/d, s.c., 2 d/wk)  Monotherapy with DFO (20 to 60 mg/kg/d 5 to 7 d/wk)	DFP and DFO: 30/29 DFO alone: 30/30  M and F  Transfusion-dependent thalassemia major and had previously received therapy with DFO	<p>Over 12 months, the alternating regimen (<math>n = 29</math>) and the standard regimen of s.c. DFO infusion (<math>n = 30</math>) showed comparable reductions in serum ferritin (<math>-248 \pm 791 \mu\text{g/L}</math> for the alternating doses of DFP and DFO arm vs. <math>-349 \pm 573 \mu\text{g/L}</math> for the DFO arm; <math>p = 0.5802</math>). Rates of therapeutic compliance did not differ between the two regimens. Trend analyses for serum ferritin revealed no significant differences between the two arms (<math>p = 0.9808</math>), but overall, there was a significant negative trend of serum ferritin concentration over time (<math>p = 0.0469</math>). The rate of decline was estimated to be <math>-24.8 \pm 12.4 \text{ mg/L/month}</math> (mean <math>\pm</math> SD). Reductions in LIC (<math>-65 \pm 615</math> vs. <math>-239 \pm 474 \mu\text{g/g}</math>) were not statistically significantly different between the alternating doses of DFP and DFO and DFO monotherapy cohorts (<math>p = 0.2263</math>). Splenectomy status, baseline serum ferritin concentration, and study site had no significant effect on similarity of efficacy between the two treatment arms.</p> <p>There was similar incidence of AEs in both groups, although gastrointestinal symptoms were more prominent in the alternating doses of DFP and DFO arm, and headache, back pain, and dysmenorrhea were more evident in the DFO only arm. No significant changes in laboratory values were found.</p>
Borgna-Pignatti et al. (Blood 2006)  5.3.5.4	7; Italy  Jan 1995; Dec 2003;  Retrospective data collected over an 8-year period	Retrospective, natural history  To compare the occurrence of cardiac disease in patients treated only with DFO to those whose therapy was switched to DFP during the period of observation, from 31 Jan 1995 to 31 Dec 2003	DFP: oral; 25 mg/kg body weight t.i.d.  DFO: s.c.; 30 to 50 mg/kg/d, 5 to 6 times per week	DFP: 157; DFO: 359  M and F  All patients treated for thalassemia major at the seven centers participating in this study, born between 1970 and 1993, who had their last follow-up between 31 Jan 1995 and 31 Dec 2003	<p>Fifty-two cardiac events, including 15 cardiac deaths, were recorded in 14.5% of subjects treated only with DFO. By contrast, during the 9-year period of this study, no subject treated with DFP developed cardiac disease<sup>(18)</sup>. To estimate the significance of the difference in occurrence of cardiac disease between the two treatment groups, the authors artificially created one cardiac event in a DFP patient. With the addition of this artificial case, the hazard ratio for DFP compared with DFO was 0.09 (CI 0.013, 0.66; <math>p = 0.017</math>).</p> <p>Six subjects given DFP for periods ranging from 3 months to 5 years had cardiac events after completion of DFP treatment. One subject had an event 20 months after stopping DFP, and the remaining five had cardiac events more than 3 years after stopping DFP.</p> <p>Fifteen patients, all on DFO, died of iron-induced cardiac disease during the review period. Cox regression analysis of total deaths did not show a significant difference in deaths between the two therapy groups (<math>p = 0.19</math>), which was not unanticipated, given the relatively low number of events. When the noncardiac deaths (i.e., the two such deaths in patients on DFP) were included as failure events in addition to the cardiac events, Cox regression analysis provided an estimated hazard ratio of a cardiac event or death of 0.078 (CI 0.010, 0.56; <math>p = 0.011</math>) on DFP relative to DFO.</p>

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 NDA 21825  
 Ferriprox (deferiprone)

Study ID Location in Module 5	Centers Location(s)  Study Start; Study End; Study Duration	Design Control type  Primary Objective	Study and Control Drugs Dose, Route, and Regimen	No. of Subjects by Arm (Entered/ Completed) Sex (M/F) Diagnosis Inclusion Criteria	Major Findings
LA-01  5.3.5.4	3; Canada  Oct 1993; Jun 1998; 2 years	Multicenter, open-label, randomized, active control  To compare the relative effectiveness and safety of DFP and DFO therapy, as reflected by the ability of each chelator to achieve net negative iron balance, reduce tissue iron stores, and reduce body iron stores	DFP: oral; 25 mg/kg body weight t.i.d. DFO: 50 mg/kg infused s.c. over 8 to 12 hours 4 to 7 times per week	DFP: 35/27 DFO: 36/30  M and F  Homozygous $\beta$ -thalassaemia	There was no significant difference (p = 0.8426) in the change in LIC (combined SQUID (preferentially over biopsy values) and biopsy analysis) from baseline (8.54 $\pm$ 3.64 mg/g, n= 13 vs. 7.09 $\pm$ 4.06 mg/g, n= 13) to Month 24 (8.90 $\pm$ 2.83 mg/g, n= 13 vs. 7.78 $\pm$ 4.68 mg/g, n= 13) between the DFP group (0.36 $\pm$ 4.87 mg/g, n= 13) and the DFO group (0.69 $\pm$ 3.40 mg/g, n= 13). Similarly, the results in LIC from baseline to Month 36 were not significantly different from zero in both groups. There was no significant difference (p = 0.6235) in the change of LIC (SQUID alone analysis) between the DFP group (2.03 $\pm$ 4.67 mg/g, n= 9) and the DFO group (1.04 $\pm$ 3.31 mg/g, n= 8). There was no significant difference (p = 0.3573) in the change of LIC (biopsy alone analysis) between the DFP group (-0.86 $\pm$ 2.71 mg/g, n= 4) and the DFO group (-3.14 $\pm$ 3.28 mg/g, n= 3). Similarly, the results in LIC from baseline to Month 36 were not significantly different from zero in both groups.  The serum ferritin levels in DFO and DFP subjects increased from baseline (2190 $\pm$ 1450 $\mu$ g/L, n= 20 vs. 1975 $\pm$ 1107 $\mu$ g/L, n= 21) to Month 24 (2294 $\pm$ 1251 $\mu$ g/L, n= 20 vs. 2192 $\pm$ 1092 $\mu$ g/L, n= 21). There was no significant difference in the change of serum ferritin (105 $\pm$ 1217 $\mu$ g/L, n= 20 vs. 217 $\pm$ 920 $\mu$ g/L, n= 21) between DFO and DFP subjects (p = 0.7408).  The change in urinary iron excretion from baseline to Month 24 was not different between DFO and DFP subjects (p = 0.9849).  From baseline to Month 12, the mean change in LVEF at rest was 6.1 $\pm$ 10.6% (n= 21) in DFP subjects and 1.2 $\pm$ 6.8% (n= 20) in DFO subjects. Only the change in DFP subjects differed significantly from zero (p = 0.0155); however, the difference between the two treatment groups was not statistically significant (p = 0.0893). From baseline to Month 24, the mean change in LVEF at rest was 8.5 $\pm$ 10.4% (n= 13) in DFP subjects and 0.9 $\pm$ 9.7% (n= 10) in DFO subjects. Only the change in the DFP subjects differed significantly from zero (p = 0.0123), but the difference between the two treatment groups was not statistically significant (p = 0.0879).  Two DFP-treated subjects experienced agranulocytosis, as defined by an ANC $<$ 0.5 $\times$ 10 <sup>9</sup> /L. Both subjects recovered fully after discontinuing the drug and treatment with granulocyte colony-stimulating factor.

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LA-03  5.3.5.4	2; Canada  Nov 1989; May 1996;  ApoPharma involved 2.5 years	Multicenter, open-label, uncontrolled  To assess the long-term efficacy and safety of DFP in patients with thalassaemia and iron overload	DFP: oral; 25 mg/kg body weight t.i.d. for 2.5 years (in some subjects treatment continued up to 4 years)	25/11  M and F  Thalassaemia major (n = 23), with iron overload and/or unable or unwilling to take DFO. Thalassaemia intermedia (n = 2)	There was a significant decrease in mean serum ferritin levels over time. On average, there was a significant decrease of 1,868.0 $\pm$ 2,898.9 $\mu$ g/L from baseline to the last observation of subjects (p = 0.0044). A majority (79%, 19/24) of subjects exhibited a decreasing trend of SF that was confirmed by the overall trend analysis (slope $\pm$ SE: -26.6 $\pm$ 11.0 $\mu$ g/L/mo, p = 0.0159). There was a significant decrease (5.7 $\pm$ 6.6 mg Fe/g dw liver, p = 0.0014) in mean LIC from baseline to the last observation of the subjects. There was a statistically significant decreasing trend in LIC levels (slope $\pm$ SE: -0.16 $\pm$ 0.04 mg Fe/g dw liver per month, p = 0.0004).  No deaths or SAEs were observed. Two subjects experienced AEs (polyarticular arthritis and severe nausea) that resulted in discontinuation of the drug and withdrawal from the study.
LA-04/06B*  5.3.5.4	31; Canada, Italy, United States  May 1996; Ongoing	Multicenter, open-label, ongoing, compassionate-use program  To provide patients with thalassaemia or other chronic iron overload conditions unable or unwilling to take DFO with an alternative treatment to control iron overload.	DFP: oral; 25 mg/kg body weight t.i.d.	96/NA  (22 subjects transferred in 1998 to the Italian Ministry of Health Controlled Release Program; 30 subjects ongoing)  M and F  Subjects with Thalassaemia major (n = 67) or other chronic iron overload conditions who required iron chelation and who were unable or unwilling to take DFO; myelodysplasia (n = 11), sickle cell disease (n = 3), myelofibrosis (n = 4), other (n = 11)	DFP treatment was able to control the body iron load, as measured by serum ferritin concentration over time.  The LIC of 25 subjects was measured at baseline, but it was not measured after treatment in any subject.

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LA-11 5.3.5.4	1; Thailand  Apr 2000 Dec 2002;  From 5 to 536 days (mean: 334 ± 179 days)	Open-label, treated with DFP alone, uncontrolled  To study the efficacy and toxicity of DFP in subjects beta-thalassemia/hemoglobin E diseases in Thailand.	DFP: 25 to 50 mg/kg/d	24/20 (treated for greater than 3 months)  M and F  Non-transfusion-dependent or irregularly transfused subjects with beta-thalassemia/hemoglobin E disease	DFP significantly reduced body iron load. After a mean treatment period of 334 ± 179 days (range 5 to 536 days), mean serum ferritin in 20 subjects who had at least two assessments (before the start, and at the end of treatment) decreased from 3,287 ± 1,927 µg/L to 1,221 ± 1,667 µg/L (mean change of -2,066 µg/L; p < 0.0001). LIC, analyzed in 16 subjects treated with DFP for more than 1 year, declined from 20.1 ± 8.4 mg/g dw liver to 7.5 ± 7.0 mg/g dw liver, with a mean change of 12.6 mg/g dw liver (p < 0.0001).  No cases of agranulocytosis occurred. One subject died during the study period as a result of septicemia with severe diarrhea after food poisoning. The investigator considered the death was not related to DFP.
LA15-0002 5.3.5.4	1; Iran  Jul 2000; Nov 2000; 3 months	Single center, open-label, Uncontrolled  To monitor the efficacy and safety of DFP for the treatment of iron overload in subjects with transfusion-dependent thalassemia, as reflected by: (1) serum ferritin concentrations; (2) the occurrence of AEs	DFP: oral: 25 mg/kg body weight i.d. for 3 months	32/26  M and F  Transfusion-dependent β-thalassemia; Previously treated with DFO (50 mg/kg/d, on average 5 d/wk) for a minimum of 7 years	Before administration of DFP, all subjects were treated with DFO (50 mg/kg/d, on average 5 d/wk) for at least 7 years. DFP reduced serum ferritin levels in all subjects. Summary data revealed a statistically significant decline in baseline serum ferritin from 3,364 ± 900 µg/L at baseline to 1,271 ± 302 µg/L after 3 months of treatment with DFP (p = 0.0001).  One subject experienced mild neutropenia (ANC = 1.45 × 10 <sup>9</sup> /L) and an unconfirmed neutropenia was detected in another subject. No unexpected ADRs were observed in this study.
LA17-9701	86; Italy  Jul 1997; Jul 2000; 3 years	Multicenter, open-label, uncontrolled, active drug surveillance study  To provide a program to control the distribution of DFP and to evaluate the long-term safety and efficacy of DFP use in subjects with TM.	DFP tablets; Oral, 75 mg/kg body weight in three divided doses before meals	532 / NA (151 completed 3 years of therapy with DFP with no missing data at the evaluated time points)  M and F  Transfusion-dependent TM and serious toxicity with DFO therapy.	DFP (75 mg/kg/d) effectively reduced serum ferritin concentrations. Declines from baseline levels reached statistical significance after 36 months of therapy (p = 0.01). In particular, declines were statistically significant at all time points (p < 0.001) for the subgroup with ferritin levels greater than 4,000 µg/L at start of treatment, while the subgroup with baseline ferritin levels of between 2,000 and 4,000 µg/L showed a significant decrease (p < 0.001) after 24 months of treatment. Analysis of changes in circulating ferritin by means of shift tables showed that only 20% of subjects passed to a more severe class of ferritin level (Class I: < 2000 µg/L; Class II: ≤ 2000 µg/L to < 4000 µg/L; Class III: > 4000 µg/L) at 12 months. The most serious ADR was agranulocytosis, which was observed in five (0.9%) subjects. All five episodes resolved upon interruption of therapy with DFP.

Type of Study	Study Number	Objectives of Study	Study Design and Type of Control	Test Products, Dosage Regimens, and Route of Administration	Number of Subjects	Subject Population	Duration of Treatment	Study Status
Comparative safety study	LA10-9902	To determine if there is a significant change in the frequency of chromosomal aberrations in circulating lymphocytes in thalassemia major subjects receiving DFO therapy following a switch in therapy to DFP, and to compare that frequency in subjects switched from DFP to DFO.  To determine the frequency of chromosomal aberrations in circulating lymphocytes in thalassemia major subjects following long term therapy with DFP compared to those on long term DFO therapy.	Open-label, crossover, active-controlled	Group 1: Ferriprox for full transfusion cycle (75 mg/kg/d, 7 days/week); switch to DFO (20 to 60 mg/kg/d, 4 to 7 days/week) for the next transfusion cycle.  Group 2: DFO for full transfusion cycle (20 to 60 mg/kg/d, 4 to 7 days/week); switch to Ferriprox (75 mg/kg/d, 7 days/week) for the next transfusion cycle.  Ferriprox: oral DFO: subcutaneous infusion	Group 1: 10 Group 2: 10	Patients with transfusion-dependent thalassemia major. Patients in Group 1 had been receiving Ferriprox for five years at the time of enrollment in this study. Patients in Group 2 had been receiving DFO for a minimum of 5 years prior to enrollment in this study.	At least 20 days  Overall subject-years: 1.56	Completed
PK in hepatic impairment	LA14-9907	Steady-state PK, metabolism, and urinary excretion.	Open-label	500-mg DFP tablets; single dose of 25 mg/kg; oral; administered at steady state.	6*	Patients with thalassemia major and cirrhosis	Single-dose/ steady state	Completed

The cut-off date for the Integrated Summary of Safety was August 31, 2006. The sponsor has submitted additional safety data in its 2007 and 2008 annual reports to IND 45724.

The sponsor has further characterized the integrated analyses by assigning the data into 9 pools (the first 2 of which the sponsor considers to be most important) that they state create data sets for a number of domains, including exposure, disposition, demographics, adverse events, laboratory studies, examination and concomitant medications. All subjects exposed to at least one dose of deferiprone are included in the overall safety data set. The sponsor's Pool 1 contains

all clinical studies of deferiprone except for 2 studies in healthy volunteers (LA 20-BA and LA 21-BE) and 1 single dose study (LA 14-9907).

Study LA 20-BA was a bioavailability study of tablet compared to liquid formulations of deferiprone. Fifteen (15) healthy volunteers were treated with a single dose of 1500 mg of deferiprone in either the tablet or liquid form. Adverse reactions included fatigability, headache, somnolence, nausea and loose stools. Study LA 21-BE was a bioequivalence study comparing the tablet and liquid formulation of the drug. Forty two (42) healthy volunteers received a single dose of 1500 mg of each formulation of deferiprone. Adverse reactions included fatigue, feeling cold and headache. Study LA 14-9907 was a PK study in thalassemia patients with cirrhosis in which 6 subjects received a single dose of 25 mg/kg of deferiprone. There was 1 adverse reaction (hyperglycemia prior to drug administration treated with insulin) that was not related to deferiprone. This safety review contains no other information about these 3 studies and uses the sponsor's Pool 1 as the source of data for review.

### 7.1.2 Categorization of Adverse Events

Adverse reactions were defined as any untoward occurrence (physical finding, symptom or laboratory finding) in a patient or subject administered a pharmaceutical product irrespective of causal relationship with the treatment. The investigator determined causality, relationship to drug and severity for adverse reactions.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data were provided individually and by pooling for the various studies that included safety data. Since most of the studies were single arm, it is not possible to compare the frequencies of adverse reactions between deferiprone and either a comparator or a placebo. Deferoxamine was the only comparator used in any of the clinical trials.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Almost all of the patients studied had thalassemia as the base diagnosis for which transfusion therapy was given (88% of all patients in all pools with transfusional iron overload). A few

patients had other transfusion dependent anemias. The estimated total exposure to deferiprone, including in postmarketing, was approximately 16,000 patient-years based on a dose of 75 mg/kg/d and an average patient weight of 60 kg. Exposure during clinical trials totaled 998 patient years with an average of  $2.2 \pm 2.2$  years per patient. The exposure times in other studies have little relevance because they did not collect safety data in a coherent manner.

The dose of deferiprone that was used in the overwhelming majority of patients was 75 mg/kg/d. The major exception was in Study LA 16-0102, in which the dose was escalated to 100 mg/kg/d by the eighth week of the trial. However, there were only 29 patients treated with deferiprone in that trial.

There was a small number of patients who participated in more than 1 study, but each was counted as a single individual in the analyses. These were primarily patients enrolled in LA 01, LA 02 and LA 03 who transitioned to LA 04, and patients in LA 02 who temporarily participated in LA 10.

There were 96 patients who were enrolled in the compassionate use study (LA 04/06B) and 30 of them were still on that study at the time of data cut-off.

A summary of overall exposure to deferiprone (and deferoxamine) from company-sponsored and investigator-driven studies (i.e., Pool 1) is shown in the following table.

Dose and Duration of Therapy with Deferiprone

	DFP 50 mg/kg/d	DFP 75 mg/kg/d	DFP 100 mg/kg/d	DFP (all doses)	DFO	Alternating Doses of DFP and DFO
Subjects exposed [N]	24	374	29	456	118	29
Subject-years of exposure	26	916	27	998	129	28
Duration of exposure (years)						
N	24	374	29	456	118	29
Mean	1.08	2.45	0.94	2.19	1.10	0.96
SD	0.560	2.326	0.202	2.184	0.741	0.041
Median	1.23	1.94	0.98	1.18	0.99	0.98
Min., max.	0.0, 1.6	0.0, 11.0	0.1, 1.1	0.0, 11.0	0.1, 2.7	0.9, 1.1
Duration of exposure [n (%)]						
Any Exposure	24 (100.0)	374 (100.0)	29 (100.0)	456 (100.0)	118 (100.0)	29 (100.0)
≥1 day	24 (100.0)	374 (100.0)	29 (100.0)	456 (100.0)	118 (100.0)	29 (100.0)
≥1 week	24 (100.0)	373 (99.7)	29 (100.0)	455 (99.8)	118 (100.0)	29 (100.0)
≥1 month	21 (87.5)	357 (95.5)	29 (100.0)	436 (95.6)	108 (91.5)	29 (100.0)
≥6 months	19 (79.2)	269 (71.9)	27 (93.1)	344 (75.4)	96 (81.4)	29 (100.0)
≥1 year	16 (66.7)	220 (58.8)	10 (34.5)	249 (54.6)	46 (39.0)	3 (10.3)
≥2 years	0	186 (49.7)	0	186 (40.8)	23 (19.5)	0
≥3 years	0	125 (33.4)	0	125 (27.4)	0	0
≥4 years	0	93 (24.9)	0	93 (20.4)	0	0
≥5 years	0	75 (20.1)	0	75 (16.4)	0	0
≥6 years	0	18 (4.8)	0	18 (3.9)	0	0
≥7 years	0	8 (2.1)	0	8 (1.8)	0	0
≥8 years	0	8 (2.1)	0	8 (1.8)	0	0
≥9 years	0	8 (2.1)	0	8 (1.8)	0	0
≥10 years	0	7 (1.9)	0	7 (1.5)	0	0
≥11 years	0	0	0	0	0	0

Source: ISS Appendix F, Table 2.7.4.1-1.1.

Notes:

- Subjects are assigned to a treatment group on the basis of the nominal dose. Denominator for percentages is the number of subjects exposed to the study drug.
- Subjects who participated in Study LA10-9902 are counted in both 75 mg/kg/d DFP and DFO columns. Subjects who took at least one dose of DFP (25, 50, 75, or 100 mg/kg/d), including those who took the alternating doses of DFP and DFO in Study LA08-9701, are included in the “DFP (all doses)” column.
- Subject-years of exposure is calculated as ([exposure end date–exposure start date+1]-sum of interruption days)/365.25.
- 16 subjects who participated in Study LA-04/06 took alternating doses of DFP and DFO and one subject who participated in Study LA-04/06 took alternating doses of DFP and Exjade. These subjects are counted in the “DFP 75 mg/kg/d” and in the “DFP (all doses)” columns.

DFP = deferiprone; DFO = deferoxamine; ISS = Integrated Summary of Safety; max. = maximum; min. = minimum.

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The demographic profile for patients in Pool 1 is shown in the following table.

Demographic Characteristics of Patients Treated with Deferiprone

	DFP 50 mg/kg/d	DFP 75 mg/kg/d	DFP 100 mg/kg/d	DFP (all doses)*	DFO	Alternating doses of DFP and DFO
Age (years)						
N	24	374	29	456	118	29
Mean	34.3	22.0	25.2	22.6	20.4	18.7
SD	10.8	12.7	3.8	12.2	6.8	4.8
Median	32.5	19.0	25.0	19.0	20.0	20.0
Min., max.	16.0, 62.0	6.0, 77.0	18.0, 32.0	6.0, 77.0	6.0, 35.0	10.0, 26.0
Age [n (%)]						
6-11	0	31 (8.3)	0	35 (7.7)	15 (12.7)	4 (13.8)
12-15	0	73 (19.5)	0	76 (16.7)	16 (13.6)	3 (10.3)
≥ 16	24 (100.0)	270 (72.2)	29 (100.0)	345 (75.7)	87 (73.7)	22 (75.9)
Sex [n (%)]						
Male	16 (66.7)	179 (47.9)	15 (51.7)	226 (49.6)	56 (47.5)	16 (55.2)
Female	8 (33.3)	195 (52.1)	14 (48.3)	230 (50.4)	62 (52.5)	13 (44.8)
Race [n (%)]						
White	0	292 (78.1)	29 (100.0)	350 (76.8)	103 (87.3)	29 (100.0)
Black	0	2 (0.5)	0	2 (0.4)	1 (0.8)	0
Asian	24 (100.0)	29 (7.8)	0	53 (11.6)	14 (11.9)	0
Unknown	0	51 (13.6)	0	51 (11.2)	0	0

Source: ISS Appendix F, Table 2.7.4.1-7.1.

Notes:

- The “n” represents the numbers of values recorded in the data.
- Subjects who participated in Study LA10-9902 are counted in both the “DFP 75 mg/kg/d” column and the “DFO” column, and subjects who took at least one dose of DFP (25, 50, 75, or 100 mg/kg/d), including those who took the alternating doses of DFP and DFO in Study LA08-9701, are included in the “DFP (all doses)” column.

DFO = deferoxamine; DFP = deferiprone; ISS = Integrated Summary of Safety; max. = maximum; min. = minimum.

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The only studies that enrolled patients with other anemias requiring transfusion included LA 03 (Compassionate use protocol in Canada), LA 04/06B (Compassionate use protocol in Italy, United States, Canada) and LA 11 (Beta thalassemia/Hemoglobin E patients in Thailand). In total, this comprised only 55 patients who were treated with deferiprone at a dose of either 50 mg/kg/d (24 patients) or 75 mg/kg/d (31 patients). The two compassionate use protocols enrolled 58 patients with  $\beta$ -thalassemia and were the only studies that enrolled non- $\beta$  thalassemia patients. The diagnoses in these studies included patients with myelodysplastic syndrome (10 patients), myelofibrosis (4), sickle cell disease (3), and 1 each of Blackfan-Diamond syndrome, aplastic anemia,  $\beta$ -thalassemia/Hb E disease, chronic lymphatic leukemia, congenital sideroblastic anemia, erythropoietin resistant anemia, pure red cell aplasia, hemolytic anemia, thalassemia intermedia, Aase syndrome and refractory anemia.

### 7.2.2 Explorations for Dose Response

None of the studies provided data that permitted an evaluation of the dose-response relationship. The overwhelming majority of patients were treated at a dose of 75 mg/kg/d. In the “pivotal” trial, Study LA 16/0102, the administered dose of deferiprone was 100 mg/kg/d for approximately the latter 10 of the 12 months of use, preceded by an initial dose of 75 mg/kg/d for 1 month and a dose of 90 mg/kg/d for 1 month. It is possible that the 100 mg/kg/d dose was used because previous studies with a lower dose had not demonstrated a beneficial lowering of either serum ferritin or liver iron concentration.

### 7.2.3 Special Animal and/or In Vitro Testing

No special animal or In Vitro testing was submitted.

### 7.2.4 Routine Clinical Testing

Routine laboratory measurements included the following:

- Blood counts. It was early recognized that deferiprone could induce agranulocytosis. Therefore, for most studies lasting more than a few days, blood counts were to be performed at approximately every 7 day (maximum 10 days between testing) intervals.
- Serum transaminases. These were most often performed on an every 3 month frequency.
- Serum ferritin. This was used as a primary efficacy endpoint in many of the studies. In addition, it was used to discontinue deferiprone therapy when the level fell below 500 µg/L. Serum ferritin was usually performed every 3 months.
- Serum zinc levels. Deferiprone chelates zinc, albeit less avidly than iron, and may lead to depressed serum levels of zinc. Serum zinc levels were usually performed every 3 months.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

None performed.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

None performed.

## 7.3 Major Safety Results

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### 7.3.1 Deaths

Deaths that occurred in Pool 1 clinical studies are shown in the following table.

#### Reported Deaths in Clinical Studies

Unique Subject No.	Link to Subject Summary	Treatment Group	Time (days)*	Cause of Death (preferred term)	Relationship to Study Medication <sup>†</sup>
<b>Study LA-01</b>					
LA-01-61	ISS Section 6.4.1.1	DFP (75 mg/kg/d)	170 [30]	Cardiac failure congestive	Doubtful
<b>Study LA-02/06</b>					
LA-0206-604	ISS Section 6.4.2.1	DFP (75 mg/kg/d)	1706 [20]	Internal injury	Not related
<b>Study LA-04/06B</b>					
LA-04-38	ISS Section 6.4.3.1	DFP (75 mg/kg/d)	46 [7]	Cardiac failure	Doubtful
LA-04-39	ISS Section 6.4.3.2	DFP (75 mg/kg/d)	180 [29]	Multiorgan failure	Not related
LA-04-49	ISS Section 6.4.3.3	DFP (75 mg/kg/d)	2681 [23]	Post procedural complication <sup>‡</sup>	Not related
LA-04-109	ISS Section 6.4.3.4	DFP (75 mg/kg/d)	157	Cardiomyopathy <sup>§</sup>	Not related
LA-04-114	ISS Section 6.4.3.5	DFP (75 mg/kg/d)	242	Cardiac failure	Not related
LA-04-127	ISS Section 6.4.3.6	DFP (75 mg/kg/d)	302 [108]	Lung neoplasm malignant	Not related
LA-04-172	ISS Section 6.4.3.7	DFP (75 mg/kg/d)	26 [1]	Cardiac failure	Not related
<b>Study LA-11</b>					
LA-11-107	ISS Section 6.4.4.1	DFP (50 mg/kg/d)	146 [2]	Diarrhoea	Doubtful

Source: ISS Appendix F, Table 2.7.4.2-1.1.

Note: Subjects were assigned to a treatment group based on the nominal dose.

DFP = deferiprone; ISS = Integrated Summary of Safety; SAE = serious adverse event.

\* Time is the number of days that the subject had stayed on the study treatment at the time of the death. If the death occurred after discontinuation, the number of days on study treatment is displayed, followed by the number of days from the time of discontinuation to the time of death in square brackets.

† Relationship to study medication based on investigator's reported assessment of causality.

‡ The "post procedural complication" preferred term is linked to the primary SAE "fracture" for the same subject appearing in Table 2.7.4.2-2.1. The SAE and reason for death for patient LA-04-49 are two separate records.

§ The "cardiomyopathy" preferred term is linked to the SAE "sepsis" for the same subject appearing in Table 2.7.4.2-2.1.

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Two of the deaths were due to accidental trauma. Five of the deaths were due to heart failure due to iron overload, and in 4 of these deaths, the patient had evidence of cardiac disease prior to the commencement of deferiprone therapy. The other deaths were due to multiorgan failure (68 year old splenectomized male with myelofibrosis who developed pneumonia, then renal and hepatic failure. The ANC prior to use of deferiprone was 0.6 to 2.0 x 10<sup>9</sup>/L and was unchanged while receiving deferiprone); lung cancer (65 year old female with myelodysplastic syndrome, coronary artery disease, peripheral vascular disease, history of treated cancer of the breast and cervix who developed agranulocytosis after 10 months of deferiprone therapy that led to termination of treatment. One month later, she was diagnosed with non-small cell lung cancer and died 3 months later. The neutrophil count was apparently normal); and diarrhea (33 year old splenectomized male in Thailand with beta thalassemia/hemoglobin E disease who was treated with deferiprone for 5 months when he developed fever and diarrhea. His ANC was 4.48 x 10<sup>9</sup>/L. He died on the following day).

*Reviewer Comments. I have reviewed the narratives of all of the persons who died while receiving deferiprone and conclude that none of the deaths was causally related to deferiprone therapy. Of note is the fact that Patient #127 (2005APO000749) developed agranulocytosis after receiving the drug for 10 months (she was also receiving thalidomide and 5-azacitidine). She then developed lung cancer and died 4 months after discontinuation of deferiprone). Also of*

*some concern is the patient who died of diarrhea which seems to be a pretty flimsy mechanism to explain a death unless the medical management of the diarrhea was deficient.*

No deaths occurred in Study LA 16-0102 and 4 deaths occurred in Study LA 10-9907, all in patients who were receiving deferoxamine (see safety review for Study LA 10-9907). None of the deaths occurred in patients receiving deferiprone.

In Study LA 17-9701 (Active Drug Surveillance Program in Italy), of 532 patients with thalassemia treated with deferiprone for 3 to 36 months, 11 patients died (2.1%). Nine of these deaths were due to cardiac failure (all had had evidence of heart disease prior to commencement of deferiprone therapy), and 2 died in automobile accidents.

In the Borgna-Pignatti Natural History Study, of 516 enrolled patients, 26 (5%) died. Twenty-four of the deaths were in the deferoxamine-only treated patients (359 patients). Of these, 15 were due to cardiac causes and the remainder to other miscellaneous causes. In the 157 patients who were switched from deferoxamine to deferiprone, there were 2 deaths (one in an accident, probably the same patient described in Study LA 17-9701, and the other due to an infection from an indwelling catheter at which time the ANC was normal).

### 7.3.2 Nonfatal Serious Adverse Events

In Pool 1, 154 SAEs occurred in 113 (24.8%) of 456 subjects treated with deferiprone compared to 4 SAEs in 4 (4%) of 118 subjects treated with deferoxamine. When normalized for duration of study drug exposure, there were 15.4 SAEs per 100 subject-years for deferiprone compared to 3.1 per 100 subject-years for deferoxamine.

Neutropenia developed in 5.9% of deferiprone treated subjects (2.7 per hundred subject-years of exposure) compared to 0.8% in the deferoxamine treated subjects. Agranulocytosis, seen only in deferiprone treated subjects, occurred in 7 of 456 (1.5%) deferiprone treated patients (0.7 per hundred subject-years of exposure). All 7 patients had resolution of agranulocytosis upon discontinuation of deferiprone, and none had residual adverse effects. The frequency of neutropenia and agranulocytosis appeared to be lower in persons with thalassemia compared to those with other causes of anemia, but there were too few patients in the latter category to determine whether or not a true difference was present. Other SAEs that occurred in deferiprone treated patients on more than a single occasion included cardiac failure (5 patients), abdominal pain (4), cellulitis (3), gastrointestinal infections (3), infectious mononucleosis (3), fracture (10), diabetes (2), renal colic (2), cholecystectomy (2), knee operation (3) and splenectomy (8). One subject experienced torsades-de-pointes.

Most serious ARs required no or temporary discontinuation of therapy. However, 47 patients treated with deferiprone experienced SAEs that led to permanent discontinuation of the drug. These included neutropenia, thrombocytopenia, agranulocytosis, cardiac failure, diarrhea, nephrolithiasis, colitis, internal injury, hepatitis, unstable angina, malignant lung tumor, sepsis, torsades-de-pointes, multiorgan failure, post procedural complications, leukemia and

cytomegalovirus infection. The most common serious AR that led to discontinuation of deferiprone was the development of neutropenia (see immediately below). Of the 27 subjects who developed neutropenia, 23 had a base diagnosis of thalassemia, and 1 each had sickle cell anemia, congenital sideroblastic anemia, myelodysplastic syndrome and Blackfan-Diamond anemia.

There were small differences in the rate of SAEs in patients in Pool 1 based on duration of treatment as shown in the following table.

Rate of Serious Adverse Events by Duration of Treatment

Time when SAE Occurred	Number of Subjects Exposed*		Number of SAEs		SAE Rate (SAEs/subject)	
	DFP (all doses)	DFO	DFP (all doses)	DFO	DFP (all doses)	DFO
Within first 6 months	456	118	44	2	0.10	0.02
Between 6 months and 1 year	344	96	22	1	0.06	0.01
Between 1 and 2 years	249	46	27	1	0.11	0.02
Between 2 and 3 years	186	23	26	0	0.14	0.00
Between 3 and 4 years	125		10		0.08	
Between 4 and 5 years	93		11		0.12	
Between 5 and 6 years	75		5		0.07	
Between 6 and 7 years	18		2		0.11	
Between 7 and 8 years	8		2		0.25	
Between 8 and 9 years	8		1		0.13	
Between 9 and 10 years	8		2		0.25	

Source: ADAE.sas7bdat, ADSL.sas7bdat and ISS Appendix F, Table 2.7.4.1-1.1.

DFP = deferiprone; DFO = deferoxamine; ISS = Integrated Summary of Safety; SAE = serious adverse event.

\* Number of subjects who were exposed during the specified period (i.e., for SAEs that occurred between Years 2 and 3, subjects who were treated for a minimum of 2 years were included).

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Although the cumulative incidence of the development of SAEs was greatest during the first year of deferiprone exposure, SAEs continued to develop for as long as 9 years after commencing use of the drug.

### 7.3.3 Dropouts and/or Discontinuations

Between 1993 and 2006, 195 (42.8%) of deferiprone treated subjects in Pool 1 (compared to 7.6% of deferoxamine treated subjects) withdrew from the clinical trials supported by the sponsor because of ARs, investigator decisions, loss to follow-up, subject request or protocol violation. Of the deferiprone treated patients who were withdrawn, 63 were withdrawn because of “treatment failures” and not because of ARs.

ARs led to deferiprone discontinuation in 77 of the 195 discontinued subjects (39.5%). Sixty-three (63) of these 77 patients were enrolled in the long-term studies (LA/02/06 and LA/04/06B).

The rate of discontinuation due to ARs for deferiprone treated patients was 7.7 per 100 subject-years compared to 1.6 per 100 subject years for deferoxamine. Discontinuations because of the development of ARs continued to occur even after many years of treatment. The most common cause of discontinuation for ARs was the development of neutropenia (24 patients).

### 7.3.4 Significant Adverse Events

See below.

### 7.3.5 Submission Specific Primary Safety Concerns

See below.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

In all Pool 1 studies, patients were treated for much longer periods with deferiprone than with deferoxamine because the number of patients treated with the former drug were treated in single arm studies. Nonetheless, the number of adverse reactions (AR) in patients treated with deferoxamine was greater than in those treated with deferiprone when based on subject-years of treatment, as shown in the following table.

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Adverse Reactions associated with Treatment

Pool	DFP Treatment (All Doses)		DFO Treatment	
	Number of Adverse Events per 100 Subject-Years	Total Treatment Exposure (subject-years)	Number of Adverse Events per 100 Subject-Years	Total Treatment Exposure (subject-years)
1	638	998	892	129

Sponsor Table (truncated), SCS, page 24

Most ARs were mild to moderate in severity, and included the SOCs of gastrointestinal, general and administrative site, and infections and infestations. Other common ARs were investigations, musculoskeletal and connective tissue, nervous system and respiratory, thoracic and medistinal disorders.

“Lack of efficacy” was reported as an AR in 59/456 patients in Pool 1. These were considered by the sponsor not to have been ARs and were excluded from further analysis of safety.

ARs occurring in >5% of subjects in Pool 1 are shown in the table below.

Adverse Reactions Occurring in >5% of Subjects in Pool 1 by SOC and Treatment Dose

	DFP 50 mg/kg/d N = 24 [n (%)]	DFP 75 mg/kg/d N = 374 [n (%)]	DFP 100 mg/kg/d N = 29 [n (%)]	DFP (All doses) N = 456 [n (%)]	DFO N = 118 [n (%)]	Alternating Doses of DFP and DFO N = 29 [n (%)]
Subjects with Any AE	23 (95.8)	324 (86.6)	29 (100.0)	403 (88.4)	100 (84.7)	27 (93.1)
Subjects with Any AE Occurring in >5%	19 (79.2)	305 (81.6)	29 (100.0)	378 (82.9)	94 (79.7)	25 (86.2)
<b>Blood and Lymphatic System Disorders</b>	1 (4.2)	41 (11.0)	1 (3.4)	43 (9.4)	10 (8.5)	0
Lymphadenopathy	0	13 (3.5)	0	13 (2.9)	6 (5.1)	0
Neutropenia	1 (4.2)	28 (7.5)	1 (3.4)	30 (6.6)	5 (4.2)	0
<b>Eye Disorders</b>	1 (4.2)	22 (5.9)	3 (10.3)	28 (6.1)	5 (4.2)	2 (6.9)
Conjunctivitis	1 (4.2)	22 (5.9)	3 (10.3)	28 (6.1)	5 (4.2)	2 (6.9)
<b>Gastrointestinal Disorders</b>	16 (66.7)	196 (52.4)	20 (69.0)	244 (53.5)	37 (31.4)	12 (41.4)
Abdominal pain	1 (4.2)	63 (16.8)	4 (13.8)	70 (15.4)	11 (9.3)	2 (6.9)
Abdominal pain upper	0	65 (17.4)	9 (31.0)	76 (16.7)	10 (8.5)	2 (6.9)
Diarrhoea	7 (29.2)	45 (12.0)	7 (24.1)	63 (13.8)	5 (4.2)	4 (13.8)
Dyspepsia	0	23 (6.1)	1 (3.4)	24 (5.3)	3 (2.5)	0
Nausea	9 (37.5)	85 (22.7)	11 (37.9)	107 (23.5)	3 (2.5)	2 (6.9)
Toothache	0	47 (12.6)	3 (10.3)	53 (11.6)	9 (7.6)	3 (10.3)
Vomiting	2 (8.3)	76 (20.3)	9 (31.0)	94 (20.6)	13 (11.0)	7 (24.1)
<b>General Disorders and Administration Site Conditions</b>	3 (12.5)	173 (46.3)	7 (24.1)	187 (41.0)	36 (30.5)	4 (13.8)
Asthma	0	20 (5.3)	4 (13.8)	24 (5.3)	9 (7.6)	0
Fatigue	0	27 (7.2)	2 (6.9)	29 (6.4)	10 (8.5)	0
Feeling abnormal	0	5 (1.3)	0	5 (1.1)	10 (8.5)	0
Injection site pain	0	0	0	0	12 (10.2)	0
Pyrexia	3 (12.5)	151 (40.4)	2 (6.9)	160 (35.1)	15 (12.7)	4 (13.8)
<b>Infections and Infestations</b>	9 (37.5)	228 (61.0)	22 (75.9)	278 (61.0)	73 (61.9)	19 (65.5)
Bronchitis	1 (4.2)	31 (8.3)	2 (6.9)	34 (7.5)	3 (2.5)	0
Ear Infection	0	30 (8.0)	0	31 (6.8)	1 (0.8)	1 (3.4)
Gastroenteritis	0	11 (2.9)	3 (10.3)	15 (3.3)	7 (5.9)	1 (3.4)
Herpes simplex	0	12 (3.2)	0	12 (2.6)	6 (5.1)	0
Influenza	0	120 (32.1)	0	125 (27.4)	15 (12.7)	5 (17.2)
Nasopharyngitis	1 (4.2)	153 (40.9)	2 (6.9)	165 (36.2)	44 (37.3)	9 (31.0)
Pharyngitis	0	112 (29.9)	7 (24.1)	129 (28.3)	23 (19.5)	10 (34.5)
Pharyngotonsillitis	0	19 (5.1)	0	22 (4.8)	6 (5.1)	3 (10.3)
Rhinitis	0	17 (4.5)	6 (20.7)	25 (5.5)	6 (5.1)	2 (6.9)
Sinusitis	0	24 (6.4)	1 (3.4)	25 (5.5)	3 (2.5)	0
Tonsillitis	1 (4.2)	35 (9.4)	1 (3.4)	39 (8.6)	2 (1.7)	2 (6.9)
Upper respiratory tract infection	8 (33.3)	13 (3.5)	2 (6.9)	23 (5.0)	7 (5.9)	0
Viral infection	0	12 (3.2)	6 (20.7)	18 (3.9)	10 (8.5)	0
<b>Injury; Poisoning and Procedural Complications</b>	0	10 (2.7)	4 (13.8)	14 (3.1)	9 (7.6)	0
Transfusion reaction	0	10 (2.7)	4 (13.8)	14 (3.1)	9 (7.6)	0
<b>Investigations</b>	2 (8.3)	87 (23.3)	18 (62.1)	108 (23.7)	17 (14.4)	1 (3.4)
ALT increased	0	26 (7.0)	11 (37.9)	38 (8.3)	5 (4.2)	1 (3.4)
Biopsy liver	0	68 (18.2)	0	68 (14.9)	1 (0.8)	0
Weight decreased	2 (8.3)	0	1 (3.4)	3 (0.7)	9 (7.6)	0
Weight increased	0	4 (1.1)	12 (41.4)	16 (3.5)	6 (5.1)	0
White blood cell count decreased	0	3 (0.8)	5 (17.2)	8 (1.8)	6 (5.1)	0
<b>Metabolism and Nutrition Disorders</b>	0	18 (4.8)	9 (31.0)	27 (5.9)	0	0
Increased appetite	0	18 (4.8)	9 (31.0)	27 (5.9)	0	0
<b>Musculoskeletal and Connective Tissue Disorders</b>	5 (20.8)	108 (28.9)	15 (51.7)	131 (28.7)	37 (31.4)	3 (10.3)
Arthralgia	2 (8.3)	71 (19.0)	8 (27.6)	82 (18.0)	11 (9.3)	1 (3.4)
Back pain	3 (12.5)	65 (17.4)	12 (41.4)	82 (18.0)	29 (24.6)	2 (6.9)
Pain in extremity	0	23 (6.1)	3 (10.3)	26 (5.7)	9 (7.6)	0
<b>Nervous System Disorders</b>	0	128 (34.2)	14 (48.3)	147 (32.2)	38 (32.2)	5 (17.2)
Headache	0	128 (34.2)	14 (48.3)	147 (32.2)	38 (32.2)	5 (17.2)
<b>Renal and Urinary Disorders</b>	0	94 (25.1)	0	94 (20.6)	0	0
Chromaturia	0	94 (25.1)	0	94 (20.6)	0	0
<b>Reproductive System and Breast Disorders</b>	0	12 (3.2)	3 (10.3)	15 (3.3)	7 (5.9)	0
Dysmenorrhoea	0	12 (3.2)	3 (10.3)	15 (3.3)	7 (5.9)	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	2 (8.3)	149 (39.8)	1 (3.4)	157 (34.4)	34 (28.8)	5 (17.2)
Cough	0	119 (31.8)	0	123 (27.0)	25 (21.2)	4 (13.8)
Pharyngolaryngeal pain	2 (8.3)	83 (22.2)	1 (3.4)	88 (19.3)	18 (15.3)	2 (6.9)

Source: ISS Appendix F, Table 2.7.4.2-13.1 and Table 2.7.4.2-6.1.

Note: Subjects are assigned to a treatment group based on the nominal dose. Denominator for percentage is the number of subjects exposed to the study drug. Events are counted once per system organ class and preferred term.

AE = adverse event; ALT = alanine transaminase; DFO = deferoxamine; DFP = deferiprone; ISS = Integrated Summary of Safety.

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Approximately 50% of ARs developed in the first month after commencing administration of deferiprone, and appeared to be somewhat earlier with higher doses of deferiprone. Almost all ARs developed during the first year of treatment.

Agranulocytosis (absolute neutrophil count (ANC) <0.5 x 10<sup>9</sup>/L) was the clinically most significant adverse reaction that occurred. In Pool 1, agranulocytosis occurred in 7/456 (1.5%) of patients treated with deferiprone. This corresponds to an overall rate of 0.7 per 100 subject-years of exposure (0.4 per 100 subject-years for thalassemia patients, 4.6 per 100 subject-years

of exposure for other iron overload conditions). In the comparator (deferoxamine) treated patients, there were no episodes of agranulocytosis. Agranulocytosis developed in persons age 11 to 64 years and in 6 females and 1 male. The mean time of onset was 0.4 years (range, 0.3 to 9.2 years). In 5/7 subjects, agranulocytosis followed a period of neutropenia. Resolution of agranulocytosis occurred in all patients (6 were treated with G-CSF), and the mean duration of agranulocytosis was 9 days (range, 3 to 85 days). The features for agranulocytosis are shown in the following table.

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Agranulocytosis in Deferiprone Treated Patients in Pool 1

Primary Disease	Number of Subjects n (%)	Number of Subjects with Agranulocytosis n (%) <sup>a</sup>	Median Age (years) [min.; max.]	Sex (male/female)	Median Time to Event in Years [min.; max.]	Median Duration of Event in Days [min.; max.]	Median Duration of DFP Therapy (days) [min.; max.]	Total Exposure (subject-years)	Rate of Events/100 Subject-Years	Hepatitis C Y/N/Unk	Splenectomy Y/N/Unk	G-CSF Y/N/Unk
Thalassemia major	401 (87.9)	4 (1.0)	14 [11; 18]	0/4	0.4 [0.3; 9.2]	7.0 [3; 9]	130 [80; 3329]	932.4	0.4	2/2/0	1/1/2	4/0/0
Non-thalassemia major	55 (12.1)	3 (5.5)	58 [12; 64]	1/2	0.8 [0.4; 1.6]	16 [9; 83]	302 [181; 1393]	65.2	4.6	0/2/1	1/2/0	2/2/0
Total	456 (100.0)	7 (1.5)	17 [11; 64]	1/6	0.4 [0.3; 9.2]	9.0 [3; 85]	181 [80; 3329]	997.6	0.7	2/4/1	2/3/2	6/2/0

Source: ADAE.sas7bdat and ADSL.sas7bdat.

Note: DFP dose = 75 mg/kg/d.

G-CSF = granulocyte colony-stimulating factor; DFP = deferiprone; max. = maximum; min. = minimum; N = no; Unk = unknown; Y = yes.

<sup>a</sup> Denominator for percentage is the number of subjects exposed to the study drug during exposure period.

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Neutropenia (ANC between 0.5 and 1.5 x 10<sup>9</sup>/L) occurred in 6.6% of deferiprone treated patients in Pool 1 compared to 4.2% of patients treated with deferoxamine.

Adverse reactions believed to be related to drug treatment were less frequent in patients treated with deferiprone compared to deferoxamine when normalized by subject-years of exposure in Pool 1 as shown in the following table.

Number of ADRs per 100 Subject-Years in Pool 1

Pool	DFP Treatment (All Doses)		DFO Treatment	
	Number of Adverse Drug Reactions per 100 Subject-Years	Total Treatment Exposure Time (subject-years)	Number of Adverse Drug Reactions per 100 Subject-Years	Total Treatment Exposure Time (subject-years)
1	138.7	997.6	201.9	129.3

Adapted from Sponsor Report, SCS, page 36

SOC categories of ADRs were gastrointestinal, general, administrative site, investigations, musculoskeletal, connective tissue, nervous system, respiratory, thoracic and mediastinal disorders. ADRs are shown in the following table.

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ADRs Occurring in >5% of Subjects by SOC in Pool 1

	DFP 50 mg/kg/d N = 24 [n (%)]	DFP 75 mg/kg/d N = 374 [n (%)]	DFP 100 mg/kg/d N = 29 [n (%)]	DFP (All doses) N = 456 [n (%)]	DFO N = 118 [n (%)]	Alternating Doses of DFP and DFO N = 29 [n (%)]
Subjects with Any ADR	9 (37.5)	234 (62.6)	27 (93.1)	277 (60.7)	48 (40.7)	7 (24.1)
Subjects with Any ADR Occurring in >5%	9 (37.5)	197 (52.7)	24 (82.8)	236 (51.8)	25 (21.2)	6 (20.7)
<b>Blood and Lymphatic System Disorders</b>	1 (4.2)	24 (6.4)	1 (3.4)	26 (5.7)	1 (0.8)	0
Neutropenia	1 (4.2)	24 (6.4)	1 (3.4)	26 (5.7)	1 (0.8)	0
<b>Gastrointestinal Disorders</b>	9 (37.5)	84 (22.5)	17 (58.6)	116 (25.4)	3 (2.5)	6 (20.7)
Abdominal pain upper	0	27 (7.2)	7 (24.1)	36 (7.9)	1 (0.8)	2 (6.9)
Nausea	9 (37.5)	55 (14.7)	11 (37.9)	77 (16.9)	0	2 (6.9)
Vomiting	2 (8.3)	42 (11.2)	8 (27.6)	57 (12.5)	2 (1.7)	5 (17.2)
<b>General Disorders and Administration Site Conditions</b>	0	0	0	0	11 (9.3)	0
Injection site pain	0	0	0	0	11 (9.3)	0
<b>Investigations</b>	0	20 (5.3)	11 (37.9)	32 (7.0)	4 (3.4)	1 (3.4)
ALT increased	0	20 (5.3)	11 (37.9)	32 (7.0)	4 (3.4)	1 (3.4)
<b>Musculoskeletal and Connective Tissue Disorders</b>	1 (4.2)	44 (11.8)	8 (27.6)	53 (11.6)	11 (9.3)	0
Arthralgia	1 (4.2)	40 (10.7)	8 (27.6)	49 (10.7)	4 (3.4)	0
Pain in extremity	0	10 (2.7)	3 (10.3)	13 (2.9)	7 (5.9)	0
<b>Nervous System Disorders</b>	0	8 (2.1)	7 (24.1)	15 (3.3)	6 (5.1)	0
Headache	0	8 (2.1)	7 (24.1)	15 (3.3)	6 (5.1)	0
<b>Renal and Urinary Disorders</b>	0	94 (25.1)	0	94 (20.6)	0	0
Chromaturia	0	94 (25.1)	0	94 (20.6)	0	0

Source: ISS Appendix F, Table 2.7.4.2-15.1 and Table 2.7.4.2-4.1.

Note: Subjects are assigned to a treatment group based on the nominal dose. Denominator for percentage is the number of subjects exposed to the study drug.

Events are counted once per system organ class and MedDRA term. ADRs occurring in >5% of subjects of the DFP (all doses) or the DFO treatment groups are presented. AEs that were reported as having definite, suspected, related, probable, and possible relationship to the treatment are considered as ADRs.

ALT = alanine transaminase; ADR = adverse drug reaction; DFP = deferiprone; DFO = deferoxamine; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Affairs.

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The frequency of ADRs associated with deferiprone (overall, 60.7%) was dose related (93.1% with a dose of 100 mg/kg/d, 62.6% with a dose of 75 mg/kg/d and 37.5% with a dose of 50 mg/kg/d) Most of the ADRs were mild (24.8%) or moderate (28.9%) in severity, with 6.6% being severe. Most ADRs occurred within the first 2 years of deferiprone use, and the time to occurrence was shorter at higher doses of deferiprone.

Gastrointestinal ADRs (nausea, vomiting, abdominal pain) occurred in 25.4% of deferiprone treated patients and appeared to be dose related but often resolved without discontinuation of therapy. Nonetheless, 2.2% of patients discontinued deferiprone because of gastrointestinal ARs.

Musculoskeletal ADRs (arthralgia, back pain, extremity pain) occurred in 11.6% of deferiprone treated patients and might have been dose related. The median time for the development of skeletal ARs was 0.5 years. Six patients (1.3%) discontinued deferiprone because of musculoskeletal ARs.

Reddish discoloration of the urine occurred in 20.6% of deferiprone treated patients and often was consistent or sporadic, rather than remitting.

## 7.4.2 Laboratory Findings

Clinical laboratory evaluations included serum alanine transaminase (ALT), absolute neutrophil count (ANC), creatinine, zinc and platelet count.

- Serum ALT levels. In Pool 1, 6.4% of patients treated with deferiprone developed ALT levels greater than 2 x ULN on 2 or more successive occasions compared to 1.7% of deferoxamine treated patients. Serum ALT levels exceeded 5 x ULN in 0.4% of patients treated with deferiprone while none of the deferoxamine treated patients exceeded that level. For Study LA 16-0102, elevations in serum ALT are shown in the following table.

Comparison of Number of Subjects with ALT Concentrations Exceeding Two or Three Times ULN between Deferiprone and Deferoxamine Treated Patients

	Randomized Treatment Groups									
	Baseline		3 Months		6 Months		9 Months		12 Months	
	DFP [n=29]	DFO [n=32]	DFP [n=28]	DFO [n=31]	DFP [n=28]	DFO [n=30]	DFP [n=27]	DFO [n=29]	DFP [n=29]	DFO [n=32]
ALT >= 2 times ULN										
No. of Subjects	4	7	8	5	6	5	4	4	6	6
Percent	13.8%	21.9%	28.6%	16.2%	21.4%	16.7%	14.8%	13.8%	20.7%	18.8%
p-value*	0.5138		0.3483		0.7437		1.0000		1.0000	
ALT >= 3 times ULN										
Number of Subjects	0	0	2	2	5	1	3	1	3	4
Percent	0.0%	0.0%	7.1%	6.5%	17.9%	3.3%	11.1%	3.5%	10.3%	12.5%
p-value*	0.0		1.0000		0.0968		0.3434		1.0000	

Source: LA16-0102 Study Report.

ALT = alanine transaminase; ULN = upper limit of normal.

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A total of 5/456 (1.1%) of deferiprone treated patients were discontinued from the drug because of an increase in serum ALT.

Elevations in serum ALT at rates of 23 to 66% associated with the administration of deferiprone has also been reported in the literature. In Study LA 17-9701 (the Italian Ministry of Health Active Surveillance Program), of 532 patients enrolled, 15 (2.8%) had elevations in ALT and 5 patients (0.9%) were discontinued from the drug because of elevation of ALT.

- ANC. Patients treated with deferiprone had blood counts performed weekly or biweekly. As noted above, in Pool 1 patients, an ANC of  $<0.5 \times 10^9/L$  developed in 7/456 (1.5%) of patients. Most occurred within the first year of exposure, but others occurred later. Discontinuation of deferoxamine in all patients and the institution of G-CSF in 6 of them resulted in resolution of agranulocytosis without residual adverse effects. Five patients received no further deferiprone. One patient was rechallenged and again developed neutropenia after 7 days, at which point the drug was stopped. One patient restarted deferiprone and developed periods of neutropenia and agranulocytosis but continued on deferiprone because it was believed that the fluctuations in ANC were not related to deferiprone.

An ANC between 0.5 and  $1.5 \times 10^9/L$  occurred in 30/456 (6.6%) of patients in Pool 1 who were treated with deferiprone, and in 5/118 (4.2%) of patients treated with deferoxamine. The onset of neutropenia in deferiprone treated patients ranged from 0.02 to 5.4 years. Discontinuation of deferiprone resulted in reversal of the neutropenia with a median time of 11 days (range, 2 to 85 days).

- Serum zinc. Approximately 4% of deferiprone treated patients developed a serum zinc level below the reference range on 2 or more consecutive measurements, but there was no sustained decrease over a long term exposure to the drug. One patient was withdrawn from drug treatment because of a low serum zinc and an associated elevation of liver enzymes.
- Creatinine. There was a shift in serum creatinine from reference range to above reference range in less than 2% of patients treated with deferiprone. One subject treated with a dose of deferiprone of 50 mg/kg/d was withdrawn from treatment for an elevated creatinine.
- Platelets. A platelet count  $<100 \times 10^9/L$  for 2 successive readings occurred in less than 1% of deferiprone treated patients. Three patients (0.7%), were discontinued from deferiprone (all were receiving 75 mg/kg/d) because of thrombocytopenia.

### 7.4.3 Vital Signs

There was insufficient appropriately collected data to provide for a meaningful analysis of the effects of deferiprone on vital signs.

### 7.4.4 Electrocardiograms (ECGs)

No thorough QTc study has been performed for deferiprone, although the sponsor proposes to conduct such a study after approval. In 2 PK studies (LA 20-BA and LA 21-BE) in healthy volunteers, mean changes in QTc intervals were -1.67 ms and +10.5 ms, respectively. In these studies, however, ECGs were performed only at baseline and at 11-25 hours after dosing. In addition, one male subject had an increase in QTc of 72 ms. This individual's ECGs were reviewed by a consulting cardiologist who opined that the waveform anomalies present were not compatible with any drug effect and could be noted in healthy volunteers. In the Pool 1 clinical trials, there is one patient reported as having experienced an episode of torsades-de-pointes. She was a 23 year old thalassemic patient who sustained residual effects from the event and was discontinued from the drug. The case was reviewed by a consulting cardiologist who stated that

the cardiac abnormality was possibly related to deferiprone. In Study LA 16-0102, 10 ECG abnormalities were observed in 9 subjects receiving deferiprone. These included ECG repolarization abnormality (3), T-wave inversion (6) and QT prolongation (1). None of these 10 events were considered serious.

#### 7.4.5 Special Safety Studies/Clinical Trials

No studies performed.

#### 7.4.6 Immunogenicity

No studies performed.

### **7.5 Other Safety Explorations**

#### 7.5.1 Dose Dependency for Adverse Events

See above.

#### 7.5.2 Time Dependency for Adverse Events

See above.

#### 7.5.3 Drug-Demographic Interactions

For deferiprone, there is some difficulty in analyzing these interactions because for many of the studies the numbers of enrolled patients were small, the studies were retrospective, the numbers of children ages 6 to 11 were very small and the race was overwhelmingly Caucasian (and with Mediterranean ethnicity). In general, gastrointestinal ARs were more common in patients less than 11 years of age compared to older patients. Patients age 12 to 15 years had a lower frequency of musculoskeletal complaints than did other age groups. There were no patients in the age 6 to 11 group who developed neutropenia (but there were only 11 total patients in that age group). Females tended to have a greater frequency of gastrointestinal ARs when compared to males. Persons of Asian descent appeared to have a lower frequency of neutropenia and gastrointestinal complaints compared to Caucasians.

#### 7.5.4 Drug-Disease Interactions

Deferiprone is metabolized in the liver and excreted by the kidney. Although deferiprone has not been formally studied in patients with renal or hepatic impairment, it may be wise to use caution when using the drug in those with functional impairment of those organs. Patients with thalassemia often have splenomegaly as the result of extramedullary hematopoiesis and this may lead to hypersplenism. Therefore, perturbations in peripheral blood counts may be difficult to interpret, particularly when the patient is receiving a drug that may cause neutropenia or thrombocytopenia. It should be noted, however, that in the limited experience provided for non-thalassemia patients, the frequency of agranulocytosis tended to be higher in patients treated with deferiprone who had non-thalassemic disorders than in those with thalassemia.

#### 7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies have been performed. In clinical studies performed with deferiprone, drugs known to be associated with the development of neutropenia were not permitted to be used. *In vitro* studies show that deferiprone does not inhibit the major human cytochrome P450 enzymes. Reports in the literature suggest that the use of combination deferiprone and deferoxamine promotes additive or synergistic iron excretion when compared to the use of deferiprone alone. Deferiprone binds to metallic cations suggesting that aluminum based antacids should not be co-administered with such drugs.

In postmarketing reports, discoloration of the urine (a common reaction related to the use of deferiprone) appeared to be diminished when the patient received concomitant all-trans retinoic acid. In another case, a female with Friedrich ataxia developed a diminished level of consciousness while receiving both deferiprone and Paludrine (proguanil/chloroquine).

### 7.6 Additional Safety Evaluations

#### 7.6.1 Human Carcinogenicity

No studies performed.

#### 7.6.2 Human Reproduction and Pregnancy Data

To date, there have been 6 reports of pregnancy in persons receiving deferiprone. Deferiprone was discontinued between the 5<sup>th</sup> and 6<sup>th</sup> of pregnancy in 3 patients (information on continued

use not available in 3). Four pregnancies produced apparently healthy offspring at term. One pregnancy terminated spontaneously, and there was no information available on the last pregnancy.

Nonclinical studies have shown that deferiprone can cause reproductive toxicity, and is therefore contraindicated during pregnancy and breastfeeding. No studies have been performed to determine whether or not deferiprone is expressed in breast milk.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

No formal studies in pediatric patients have been performed or are proposed by the sponsor. In Pool 1 clinical studies, 35 (7.7%) of the patients were between the ages of 6-11 years, and 76 (16.7%) of patients were between the ages of 12-15 years. There was no formal assessment of safety specifically based on age. In response to a request from the EMEA for additional safety data in persons younger than 10 years of age, the sponsor reported the following data from clinical studies in its Periodic Safety Update Review #12. There were no patients under the age of 6 years. There were 18 patients between the ages of 6-10 years with a total exposure of 31.85 years. These patients developed 160 ARs, with the most frequent being headache (50%), cough (50%), nasopharyngitis (44%), fever (39%), abdominal pain (33%), pharyngitis (33%), influenza (33%), arthralgia (28%), pharyngeal pain (28%), ear infection (22%), upper abdominal pain (17%), vomiting (17%), tonsillitis (17%) and chromaturia (17%). There were no cases of agranulocytosis, neutropenia or thrombocytopenia. Most of the ARs were mild (142) and 5 were severe (fever in 2 patients, lymphadenitis in 1 patient, urinary tract infection in 1 patient and arthropathy in 1 patient). Abdominal pain, chromaturia, increased appetite, arthralgia and headache were believed to be related to deferiprone. The sponsor concluded that ARs in patients between the ages of 6-10 years were similar to those seen in older populations studied in clinical trials.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Deferiprone has no known central nervous system effects that would suggest a potential for drug abuse. No studies have been performed on potential withdrawal or rebound effects. There have been 2 cases of chronic overdosing of deferiprone in postmarketing reports. The patients were ages 7 and 9 years. The 7 year old patient received approximately 250 mg/kg/d for approximately 1 year. He developed a gait disturbance. The 9 year old patient received approximately 250 mg/kg/d for 2 years and developed a cerebellar syndrome. Both events resolved after discontinuation of deferiprone.

## 7.7 Additional Submissions

The sponsor submitted a Day 120 Safety Report dated May 28, 2009 with a cut-off date of February 28, 2009. Up to the cut-off date, clinical studies that continued in progress were LA 04

and LA 06B. The sponsor submitted a completed study report (LA 30-0307: The safety of oral deferiprone in pediatric patients with thalassemia) on May 21, 2009. Patients in that study were permitted to enroll on an extension study which is still in progress (LA 28 CMP). Non-clinical studies completed during the interval include an IV study of deferiprone in monkeys, an eye irritation study in rabbits and an hERG study.

In clinical studies, the Pool 1 population has been expanded to include the subjects treated in the LA 30-0307 and LA 28 CMP trials. Therefore, the total Pool 1 population now includes 590 subjects with 1,189.3 subject-years of exposure. Of these, 4% were treated at a dose of 50 mg/kg/d, 70% at a dose of 75 mg/kg/d and 14% at a dose of 100 mg/kg/d. Other dose regimens (including in combination with deferoxamine) were administered in 12% of patients. The mean duration of therapy was 2.02 years (range, 0-13.38 years). The mean age of treated subjects was 19.8 years (range, 1-77), 220 were <age 16 years and 142 were age <12 years (including 100 subjects age 10 years or less in LA 30-0307) and there were 300 males and 290 females. Caucasians comprised 73.9% of the population, Blacks, 0.7%, Asians, 15.8% and unknown, 9.7%. The primary diagnosis was thalassemia in 513 subjects, E-thalassemia in 39, MDS in 14, myelofibrosis in 4 and sickle cell disease in 5. Splenectomy had been performed in 28.1%, 43.7% were serologically positive for hepatitis C, 21.5% had a serum ALT >2x ULN, 1.4% had an ANC of <1,500/ml and 44.7% had a serum ferritin >2,500 µg/L.

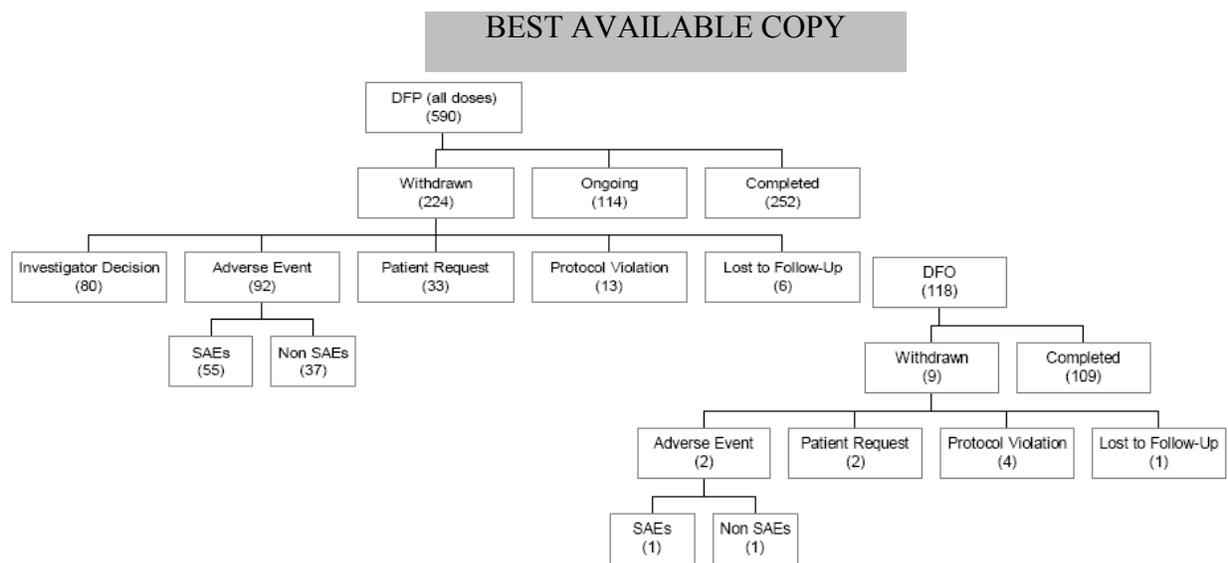
Safety analysis showed that there were 497 ARs in the 590 subjects. There did not appear to be a dose dependency on ARs except for neutropenia and arthralgia. The most common ARs were those previously reported. These included gastrointestinal ARs in 44.7% (nausea, vomiting, abdominal pain, diarrhea), chromaturia in 15.9%, arthralgia in 15.6%, fever in 12.7%, increase in ALT in 9.3%, decreased neutrophils in 8.8%, and neutropenia in 6.4%. Gastrointestinal symptoms and arthralgias appeared to be more common in persons over age 16 years compared to those less than age 16 years. Neutropenia was more common in non-splenectomized persons and in those with a primary diagnosis of non-thalassemia anemia. The median time of onset of neutropenia was 263 days (range, 8-1966 days).

Serious ARs developed in 135 (22.9%) of patients. This rate is very close to the rate reported in the Integrated Summary of Safety submitted with the NDA. Additional SARs reported since the cut-off of the ISS on August 31, 2006 that occurred in more than 1 case included neutropenia (11), CHF (5), agranulocytosis (4), atrial flutter (3), atrial fibrillation (2) and diabetic ketoacidosis (2). Most of these SARs occurred in subjects treated in LA 04/06B (Compassionate Use Protocol).

Agranulocytosis has now developed in 11/590 (1.9%) of subjects enrolled in clinical trials. Nine of these events occurred in persons receiving deferiprone at a dose of 75 mg/kg/d while the other 2 occurred in persons treated at a dose of 100 mg/kg/d. Eight of the 11 were females. Eight had a primary diagnosis of thalassemia, 2 had MDS and 1 had sickle cell disease. Nine of the episodes occurred within the first year of treatment, although one person had received deferiprone for nine years before the development of agranulocytosis. Agranulocytosis resolved (with or without the use of marrow stimulating agents) in a median of 10 days, although agranulocytosis persisted for 85 days in one person.

The sponsor received 111 SADR in post-marketing period from August 31, 2006 through cut-off on February 28, 2009. These are summarized in the section (8 Post Market Experience, below). No new safety findings were present.

In clinical studies, 224 of 590 (38%) deferiprone treated subjects were withdrawn from deferiprone therapy (29 of these withdrawals were reported in the 120 Safety Update). Of these 29, 15 were for ARs, 2 were by investigator decision, 3 were lost to follow-up, 8 were at the subject's request and 1 was for protocol violation. These are shown in the following diagram.



- 1) The disposition category from the last trial is displayed for subjects who participated in more than one trial.
- 2) Subjects exposed to more than one DFP dose are classified by their maximum dose.
- 3) There are 7 Subjects who's maximum dose of DFP is other than 60, 75 or 100, not exceeding 100 mg/kg/day. These Subjects are included in DFP (all doses)
- 4) Subject LA\_04\_240 on Alternate/Combination Therapy with DFP died from arrhythmia and cardiac failure 2 days after beingexposed to Deferiprone. The Arrhythmia and cardiac failure were pre-treatment (with DFP) events. This withdrawal is included as an SAE.

**Figure 5.1.1-1: Disposition of DFP treated subjects in Pooled Clinical Studies (Pool 1)**

The disposition of all subjects in all Pool 1 Clinical Studies is shown in the following table.

**Table 5.1.1-1 Disposition of subjects in Pooled Clinical Studies (Pool 1)**

Disposition Category	DFP 50 mg/kg/d n=25 (%)	DFP 75 mg/kg/d n=411 (%)	DFP 100 mg/kg/d n=85 (%)	DFP (all doses) mg/kg/d n=590 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination on Therapy with DFP n=62 (%)
<b>WITHDRAWALS BY AGE GROUP</b>						
1 - 5 YEARS	1 ( 4.0)	4 ( 1.0)	3 ( 3.5)	9 ( 1.5)	0 ( 0.0)	0 ( 0.0)
6 - 11 YEARS	0 ( 0.0)	17 ( 4.1)	2 ( 2.4)	21 ( 3.6)	1 ( 0.8)	1 ( 1.6)
12 - 15 YEARS	0 ( 0.0)	32 ( 7.8)	0 ( 0.0)	32 ( 5.4)	0 ( 0.0)	0 ( 0.0)
>= 16 YEARS	8 ( 32.0)	145 ( 35.3)	2 ( 2.4)	162 ( 27.5)	8 ( 6.8)	7 ( 11.3)
<b>WITHDRAWALS</b>						
TOTAL	9 ( 36.0)	198 ( 48.2)	7 ( 8.2)	224 ( 38.0)	9 ( 7.6)	8 ( 12.9)
ADVERSE EVENT	4 ( 16.0)	77 ( 18.7)	5 ( 5.9)	92 ( 15.6)	2 ( 1.7)	5 ( 8.1)
INVESTIGATOR DECISION	0 ( 0.0)	78 ( 19.0)	0 ( 0.0)	80 ( 13.6)	0 ( 0.0)	2 ( 3.2)
LOST TO FOLLOW-UP	1 ( 4.0)	5 ( 1.2)	0 ( 0.0)	6 ( 1.0)	1 ( 0.8)	0 ( 0.0)
PATIENT REQUEST	4 ( 16.0)	28 ( 6.8)	2 ( 2.4)	33 ( 5.6)	2 ( 1.7)	0 ( 0.0)
PROTOCOL VIOLATION	0 ( 0.0)	12 ( 2.9)	0 ( 0.0)	13 ( 2.2)	4 ( 3.4)	1 ( 1.6)

Of the 15 patients who were discontinued from deferiprone between August 31, 2006 and February 28, 2009, 4 were for agranulocytosis, 4 were for arthralgias, 2 were for neutropenia, and 1 each for confusional state, acute myeloid leukemia, CHF, abdominal pain and CHF due to arrhythmia. This additional information provides no new insights into safety events associated with deferiprone.

The Day 120 Safety Update adds 3 deaths that occurred in patients receiving deferiprone in clinical trials during the period from August 31, 2006 through February 28, 2009 to the 10 deaths reported in earlier clinical studies for a total of 13 deaths in all clinical studies. Ten of the thirteen deaths occurred in LA 04/06B (Compassionate Use). Of these, 7 had thalassemia, 1 had hemoglobin E-thalassemia and 5 had other diseases. Two deaths were due to motor vehicle accidents. Seven deaths were attributed to iron-induced cardiac disease, 6 of whom had cardiac disease prior to commencement of deferiprone. The other 4 deaths were due to multi-organ failure, lung cancer, acute myeloid leukemia and diarrhea.

I have reviewed the case reports of the 3 additional deaths in clinical studies. None of the deaths appear to have been related to deferiprone in any causal manner, but rather appeared to be related to the natural histories of the disease that led to the need for iron chelation therapy with deferiprone.

The Day 120 Safety Update adds 6 deaths that occurred in patients receiving deferiprone in post-marketing reports during the period from August 31, 2006 through February 28, 2009 to the 11 deaths reported in earlier post-marketing reports for a total of 17 deaths in all post-marketing reports. Patients ranged from 10 to 83 years of age. Thirteen of the deaths were due to

agranulocytosis (one with pulmonary embolism), 3 due to CHF, and 1 due to sepsis not associated with agranulocytosis.

I have reviewed the case reports of the 6 additional deaths in post-marketing reports. In the 2 cases of agranulocytosis, deferiprone therapy appeared likely to be the proximate cause of death even though 1 of the patients had a history of a failed bone marrow transplantation. In the other 4 cases, it appeared that the cause of death was due to the natural history of the underlying disease.

Abnormalities of liver function tests have been noted in clinical trials with deferiprone. With the addition of the Day 120 Safety Update, the cumulative frequency of an increase in serum ALT in subjects with normal values at baseline to >2x ULN was 12.75%, to >3x ULN was 6.4% and to >5x ULN was 1.7%. There were no reports of increased ALT/AST in post-marketing reports in the Day 120 Safety Update.

The Day 120 Safety Update shows that the cumulative frequency of an increase in serum creatinine from normal at baseline to above the normal range at the end of study was 0.89%. There were no reports of abnormal creatinine levels in post-marketing reports. For serum zinc levels, a fall from normal to below normal occurred in 12% of patients.

The Day 120 Safety Update revealed no significant changes in vital signs or physical examinations. ECGs were performed at baseline and at week 24 for the 98 children enrolled in LA 30-0307. There were no statistically significant changes that occurred in the quantitative measures determinable by ECG. The mean QT fell by  $0.97 \pm 29.0$  ms and the mean QTc fell by  $3.2 \pm 35.4$  ms. Although there were some wave form changes, these were bi-directional, and changes at the conclusion of the study (24 weeks of therapy) were due mostly to tachycardia. The ECG was consistent with LVH in one subject and with an intraventricular conduction defect in another.

Two pregnancies occurred in the partners of 2 patients with thalassemia treated with deferiprone. The offspring in one had mild hypospadias and the other had normal growth and development at age 6 months.

Non-clinical studies completed and reported in the interval between August 31, 2006 and February 28, 2009 included the following:

- Four day toxicity study in monkeys. The continuous intravenous infusion of deferiprone for 96 hours at doses targeted to provide a serum concentration of 60  $\mu\text{M}$  in 3 female cynomolgus monkeys was not associated with obvious toxicity. Increasing the infusion to target a serum concentration of 120  $\mu\text{M}$  led to death or a moribund state. Organs adversely affected included the liver, kidney, lungs, heart and spleen.
- hERG study. Deferiprone did not inhibit hERG-mediated potassium currents at concentrations of up to 3000  $\mu\text{M}$ .
- Eye irritation in rabbits. Deferiprone was neither irritative nor corrosive at concentrations of up to 12.92 mg/mL.

The Day 120 Safety Update includes 7 SARs that occurred in both clinical studies and post-marketing reports after the cut-off date through May 15, 2009. I have reviewed the case reports of all these patients. Most of the SARs appeared to be causally unrelated to deferiprone. However, there was one patient who developed neutropenia and another who developed agranulocytosis. The latter recovered upon discontinuation of deferiprone.

## 8 Postmarket Experience

Deferiprone tablets are approved in 60 countries (including the European Union), and in none of these countries has there been a regulatory action that called for the suspension or discontinuation of sales. In almost all of these countries, the indication for deferiprone is “for the treatment of iron overload in patients with thalassemia major when deferoxamine therapy is contraindicated or inadequate”. (b) (4)

Since the introduction of the drug in the marketplace, the sponsor has prepared and submitted nineteen Periodic Safety Update Reviews (PSURs) with the latest of these covering the period September 1, 2008 to February 28, 2009. The sponsor has submitted all of these PSURs to the NDA. During the last two reporting periods (covering one year of drug sales), it has been estimated that there were approximately 4,686 patient-years of exposure. Although the PSURs are primarily directed at issues of the safety of the use of deferiprone, the sponsor has also included information regarding other aspects of the drug, including efficacy results.

I have reviewed all of the PSURs and have summarized the information provided by them.

### Safety

Agranulocytosis. Since the initial trials with deferiprone, agranulocytosis has been a persistent cause of concern. Data provided by the sponsor indicates that there were 11 cases of agranulocytosis associated with the use of the drug in clinical trials conducted from 1993 until February 28, 2009. This represented a rate of 0.92 cases per 100 patient-years of exposure. From September 1, 1999 (date of first marketing authorization) through February 28, 2009, there were 83 cases of agranulocytosis associated with the use of the drug in post-marketing reporting. This represented a rate of 0.33 cases per 100 patient-years of exposure. Although there were no deaths related to agranulocytosis during the clinical trials, there have been 11 reports of death due to deferiprone-induced agranulocytosis in the post-marketing period.

On January 31, 2006, the sponsor established an expert panel to review the data on deferiprone’s relationship to agranulocytosis. To date, the sponsor has not indicated that the panel has met or completed its deliberations.

The mechanism of the development of agranulocytosis is uncertain but, in patients in whom bone marrow examinations were performed, there appeared to be an absolute or relative hypoplasia/aplasia of the myeloid series suggesting a myelotoxic effect of the drug upon the marrow. There were no specific demographic features of patients who developed agranulocytosis. Agranulocytosis does not appear to be a dose-dependent event for deferiprone. Agranulocytosis occurred in as short a period as a week and as long as several years after commencement of deferiprone. It appeared to be less common in patients who had been splenectomized. There were no reported drug-drug interactions with which it has been associated. Patients may have a prodrome of neutropenia of some duration prior to the development of frank agranulocytosis. A small fraction of patients who developed neutropenia that led to discontinuation of the drug developed agranulocytosis upon rechallenge. Although some patients were treated with granulopoietic stimulating agents and drug discontinuation with resolution, for others, cessation of drug therapy resulted in spontaneous resolution. There were no reports of long-lived agranulocytosis in any of the patients who survived the period of agranulocytosis. In general, in patients who experienced an episode of agranulocytosis, there did not appear to be an effect on red cell or platelet maturation and release, although there have been several reports of the development of isolated thrombocytopenia in patients treated with deferiprone.

In November, 2005, the sponsor submitted a Risk Management System regarding agranulocytosis to the EMEA. At the end of 2006, the sponsor distributed a Dear Health Care Professional Letter to prescribers that outlined guidance on the prevention and treatment of agranulocytosis associated with the administration of deferiprone. In addition, the sponsor distributed wallet-sized cards to patients emphasizing the importance of regular monitoring of blood counts while receiving deferiprone.

In its proposed label, the sponsor has incorporated a Box Warning regarding the development of agranulocytosis during the administration of deferiprone.

Hepatic Injury. Because of the findings reported by Oliveri and coworkers of increasing hepatic fibrosis in patients treated with deferiprone in Study LA 03, the Deferiprone International Independent Safety Monitoring Committee that oversees Studies LA 02/LA 06 commissioned a study by independent pathologists to review liver biopsies of patients participating in these studies. Three pathologists independently analyzed coded and randomly ordered samples from 56 patients using the Laennec and Ishak scoring systems for hepatic fibrosis. The mean of the three scores for each biopsy was used. The mean interval between biopsies was 3.1 years (range, 1.2-4.9 years). In 11 patients seronegative for hepatitis C, fibrosis scores before and after deferiprone therapy were  $1.12 \pm 1.07$  and  $0.97 \pm 0.84$  using the Ishak system, and  $0.71 \pm 0.65$  and  $0.70 \pm 0.53$  using the Laennec system. Among 45 patients seropositive for hepatitis C, fibrosis scores before and after deferiprone therapy were  $1.91 \pm 1.13$  and  $2.04 \pm 1.30$  using the Ishak system, and  $1.26 \pm 0.73$  and  $1.35 \pm 0.90$  using the Laennec system. None of the changes was statistically significant. (Publication. Wanless I et al. Blood 2002; 100:1566-9).

Drug-induced hepatitis associated with the administration of deferiprone has been reported (PSUR#3, 1 case with a positive rechallenge).

In clinical trials with deferiprone, an elevation in liver enzymes occurred in 6% of treated patients at a rate of 3.7 per 100 patient years of exposure.

Pancreatitis. Several cases of pancreatitis associated with the administration of deferiprone have been reported (PSUR#3, 1 case), including 1 patient who was rechallenged with deferiprone and relapsed thereupon.

Arthropathy. Has been periodically reported.

Diarrhea. In clinical trials with deferiprone, 13% of patients experienced diarrhea as an adverse reaction. Five percent (5%) of these events were severe. One case of severe diarrhea reported from Thailand ended in the death of the patient, but the patient's physician stated that the diarrhea was not related to the administration of deferiprone.

Cardiac. Torsades-de-pointes (LA 04/#088) was reported in one patient who had T wave inversion and a prolonged QT interval prior to treatment with deferiprone. The sponsor asked an external cardiologist to review the adverse reaction. The cardiologist stated that, on the basis of the Naranjo criteria, the causality of the event should be "possible". In a study of the administration of deferiprone to patients positive for HIV, adverse reactions included "non-significant" prolongation of the QT interval. The sponsor has performed a preclinical study that shows that deferiprone does not inhibit hERG-mediated potassium currents at concentrations of up to 3,000  $\mu\text{M}$ .

Auditory. Hearing loss has been reported. This adverse reaction appears to be common to all iron chelating agents.

Dermatological. Various skin reactions, including photosensitivity reactions, have been reported in association with the administration of deferiprone, but causality to the drug has not been established. Several patients who experienced dry skin showed relief after supplementation with zinc.

Neurological. A cerebellar syndrome (ataxia, diplopia, nystagmus, psychomotor delay) has been reported in patients who mistakenly received higher than recommended doses of deferiprone for long periods. The abnormalities resolved after discontinuation of the drug. A patient with Friedreich ataxia treated with deferiprone in an investigational study developed a depressed level

of consciousness that resolved upon discontinuation of the medication. Newly diagnosed epilepsy was reported in a healthy 19 year old male volunteer 5 days after completion of a trial of the administration of deferiprone at a dose of 50-150 mg/kg/d. Transient thrombocytopenia was also present. One subject in Study LA 03 developed de novo epilepsy after treatment with deferiprone at a dose of 75 mg/kg/d for 132 days. The drug was continued without recurrence of seizures.

Hematological. Several cases of isolated thrombocytopenia associated with the administration of deferiprone have been reported. No mechanism has been defined.

Immunological. One patient developed biopsy-documented Henoch-Schoenlein purpura while being treated with deferiprone. Discontinuation of the drug was associated with resolution of the disorder.

*Reviewer comments. The determination of the safety of the administration of deferiprone by the sponsor is not based on randomized control trials. Rather, it is based primarily on the basis of single arm trials and postmarketing reports. The drug is currently marketed in 60 countries worldwide and has been commercially available in a number of these countries for 10 years.*

*The main safety concerns are as follows:*

- *Agranulocytosis. This adverse reaction probably occurs in about 1% of patients receiving deferiprone. Its development is unpredictable, but in some patients follows the occurrence of neutropenia. It does not appear to be dose related, occurs at variable time intervals after commencement of deferiprone, appears to be more common in non-splenectomized patients and has not been reported to be irreversible. Cessation of therapy with deferiprone, with or without the use of myelostimulatory drugs, is associated with relief of agranulocytosis. However, deaths from sepsis have been reported during the period of agranulocytosis.*
- *Hepatic toxicity. Hepatic toxicity has been suggested because of an increase in transaminase levels in persons receiving deferiprone that improved following discontinuation of the drug and an occasional patient who had an increase in transaminase levels upon rechallenge. One investigator reported increased fibrosis in the liver after several years of treatment with deferiprone. The clinical significance of these laboratory changes is clouded because persons with iron induced hepatic toxicity often exhibit waxing and waning of transaminase levels, iron deposition may lead to hepatic injury, and patients often develop infectious hepatitis because of multiple transfusions.*
- *Gastrointestinal ARs. These include both upper and lower GI symptoms. Pancreatitis associated with the use of deferiprone has also been reported.*
- *Arthropathy. The frequency of arthropathy in patients receiving deferiprone reported in early human studies led the sponsor to investigate the possible mechanisms of arthropathy in Study LA 02. Results from that study suggest that the arthropathy is not*

*due to an immunological reaction induced by deferiprone, but no other mechanism has been proposed. The arthropathy appears to resolve with the discontinuation of deferiprone.*

- *Cardiac. Torsades-de-pointes has been reported in a one individual although the relationship to the drug has not been established.*
- *Neurological. A cerebellar syndrome has been reported in several individuals who mistakenly received excessive doses of deferiprone over long periods of time. It is possible that this type of reaction is due to the use of deferiprone in persons whose iron overload has been relieved. Such reactions have been reported in non-iron overloaded patients being treated with deferiprone for the treatment of Freidrich's ataxia.*
- *Miscellaneous. Auditory, platelet, immunological and dermatological ARs have been reported.*

In summary, the main AR to be considered in the benefit/risk assessment is the development of agranulocytosis. The other ARs reported with the use of deferiprone are either manageable, infrequent or may not be attributable to the drug itself.

## **9 Appendices**

### **9.1 Labeling Recommendations**

The sponsor has submitted the following label. I have reviewed the label and my recommendations for important changes follow each section *in italics*.

30 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

# NDC	Package Description	Multilevel Packaging
1 60505-2538-1	100 TABLET In 1 BOTTLE, PLASTIC ( BOTTLE)	None

### **9.3 Advisory Committee Meeting**

An Oncology Drugs Advisory Committee was scheduled for October 6, 2009. In mid-September, 2009, the Division of Scientific Investigation of the FDA informed the DMIHP that the audit of the LA 01 study performed in Toronto, Canada (the site in Montreal was not included) indicated that the principal investigator appeared to be adherent with the requirements of the protocol, and that it appeared that the data from that study should be considered valid in assessing the efficacy and safety of the use of deferiprone in patients with thalassemia and transfusion related hemosiderosis. The submission from the FDA investigator was voluminous, and it was believed that the document could not be analyzed completely in the short time period before the presentation to the Advisory Committee. Because there appeared to be some discrepancy between what the sponsor had submitted and what the FDA auditor may have found, it was decided that the Advisory Committee meeting scheduled for October 6, 2009 would be canceled until a future date.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	GI-1	AOPHARMA INC	FERRIPROX (DEFERIPRONE)
NDA-21825	ORIG-1	AOPHARMA INC	FERRIPROX (DEFERIPRONE)

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/s/

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GEORGE G SHASHATY  
10/19/2009

KATHY M ROBIE SUH  
10/19/2009

# MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** May 18, 2009

**FROM:** George Shashaty, M.D.  
Medical Reviewer  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products, CDER, FDA

**SUBJECT:** **Information Request**  
**Deferiprone (NDA 21825)**

**TO:** Kathy Robie Suh, M.D., Ph.D.  
Medical Team Leader  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products, CDER, FDA

## Background

NDA 21825 was submitted on January 29, 2009. I am in the process of reviewing the NDA and have the following requests for information from the sponsor:

### **For Study 16/0102**

- Provide analyses of the relationships between the measure of MRI T2\* and MRI LVEF, ECHO LVEF and ECHO LVSF. Analyses should include the degree of correlation with standard deviations and confidence intervals and timed correlations (at baseline, 6 and 12 months of the trial).
- Provide data that correlate MRI T2\* measurements with the results of quantitative chemical measurements of iron concentration in the heart.
- You have indicated that there is a difference in cardiac MRI T2\* of  $2.3 \pm 2.2$  ms in patients treated with deferiprone for 1 year. Provide evidence that this change in MRI T2\* indicates a meaningful effect of deferiprone on clinical outcomes of thalassemia patients with iron overload.
- Provide data that show that measurement of MRI T2\* allows for the diagnosis of pre-clinical iron-induced cardiac abnormalities that are a predictor of the development of clinical heart disease.

- Provide the Image Review Charter for the cardiac T2\* portion of the study that details the procedures used to acquire, display and interpret the images and to transfer the data for analysis. The charter should include a procedure for image acquisition; quality control; de-identification of data; blinding of reads; randomization of sequence; selection of an ROI; independence of the reader; and, variability of reads.
- Although the study sites were qualified initially for the performance of MRI T2\*, there are no listed procedures for verification of the reproducibility of the images over the time of the study (e.g., machine drift).
- Provide the charter for the blinded readings of the ECHO LVEF and LVSF.
- One hundred and sixty (160) patients were screened in order to enroll 61 patients on the trial. Eleven (11%) percent of screened persons were excluded because of an MRI T2\* of less than 8 ms and 2% were excluded because of a diminished LVEF. What were the MRI T2\* measurements in the patients with a diminished LVEF. Also, provide follow-up information (mortality, development of cardiac disease, etc) on the patients who were not enrolled on the trial because of a diminished MRI T2\* measurement or for a diminished LVEF.

#### **For Study 12/9907**

- For each patient who was begun on deferiprone, provide the reason as to why he/she was converted from deferoxamine at the time of commencement of the observation period.
- Provide the number of patients who were begun on deferiprone de novo before receiving any deferoxamine.
- Explain how the cardiologist was blinded to treatment assignment for each examined patient. It would appear that careful history and physical examination (needle marks, skin irritation, local hematoma) of each patient would easily allow the differentiation of those patients receiving deferoxamine from those being orally treated with deferiprone.
- It appears that for many patients, the diagnosis of clinical heart disease was based on a LVEF or LVSF that fell below some arbitrary value. Provide the measurements used by the cardiologist to calculate the LVEF and the LVSF.
- It appears that symptomatic heart disease was present in only a minority of patients. For these symptomatic patients, provide a separate analysis and discussion of demographics, treatment and outcomes.
- There were no differences from baseline to end of study in LVEF ( $70.9 \pm 7.2$  to  $69.4 \pm 6.6$  and  $69.0 \pm 7.0$  to  $69.2 \pm 8.4$ ) or LVSF ( $37.0 \pm 6.1$  to  $36.8 \pm 4.2$  and  $36.3 \pm 6.6$  to  $35.4 \pm 5.1$ ) for patients assigned to deferiprone and deferoxamine, respectively. Provide an analysis for the LVEF and the LVSF at the end of 1 year of the study. If there are no differences at the end of 1 year for Study LA/12/9907, what is your explanation for this in light of the differences observed in Study LA16/0102?
- Sixteen patients were excluded from analysis because they did not have at least 4 years of chelation therapy during the observation period. For these patients, provide the following:
  - The number receiving deferiprone and the number receiving deferoxamine with the number of days of treatment received during the observation period.

- The number of patients in each arm not receiving therapy because of adverse reactions.
- Analyses of demographic characteristics, primary and secondary efficacy endpoints, and safety evaluations for these patients.

### **For Other Submitted Studies**

- For Study LA/01, provide your own review of the liver biopsy data (which you alluded to in the briefing meeting of April 13, 2009) that you believe contradicts the conclusions of the primary investigator that led to a publication that indicated refractoriness to therapy and excess hepatic fibrosis in patients treated with deferiprone compared to patients treated with deferoxamine.
- Patients described in Study LA 12/9907, the Borgna-Pignatti report and Study LA 17/9701 appear to have a commonality of institutions from which they were selected. It appears, therefore, that some of the patients are listed as having been participants in more than one of the reports and may be duplicated. Provide a list of patients from the 3 cited studies who were enrolled in 2 of the studies, and of patients who were enrolled in all 3 of the studies.

### **Other Requests**

- In the Clinical Overview Section (Module 2, Section 2.5), on page 21, you state that “Cardiac MRI T2\*... has been approved with a CE mark in the EU for use as a Class I Medical Device, and has been approved in principle by the FDA”. Explain what a “CE mark” is and indicate its significance in regard to medical management. Explain the exact status of the cardiac T2\* methodology vis a vis the FDA.

### **Recommendations**

The information requested above should be obtained from the sponsor.

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this page is the manifestation of the electronic signature.**  
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/s/

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George Shashaty  
5/18/2009 03:10:52 PM  
MEDICAL OFFICER

Kathy Robie-Suh  
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